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EDITORIAL

Inactivation of One of the X Chromosomes in Females Is a Biological Phenomenon of Clinical Importance

sex chromosome constitution is fundamentally rent between male and female members of imalian species Females have a pair of equal hromosomes (X chromosomes) whereas males one X chromosome and one much smaller mosome the Y chromosome in the sex mosome pair The sex of the zygote is depend upon which sex chromosome is present in the oid chromosome set of the sperm cell fertilizing egg and the difference in sex chromosome con ition between male and female conceptuses is the basis for their divergent sexual differen on and development

great number of genes not related to sexual elopment are known to reside in the X chromo- ie One might have expected that the effect of h genes would be much more pronounced in iales who have two X chromosomes than in les who have only one This expectation how r does not materialize Healthy males and iales have about the same level of the enzyme cose-6-phosphate dehydrogenase (G6PD) as ll as of blood clotting factor VIII Both proteins determined by genes on the X chromosome

Vork by *Drosophila* geneticists antedates that of nmalian geneticists in this area by a good many rs The fact that X linked genes (genes on the X omosome) in *Drosophila* have a similar expres i in males and females was established at an y stage and H J Muller introduced dosage ipensation for the regulatory mechanism which eared to be operating

ess than 20 years ago Mary Lyon and other kers addressed themselves to the question of age compensation in mammals Lyon (7) studied colour patterns in mice who were heterozygous X linked genes determining these traits She forward the hypothesis that the mottling notypes caused by X linked genes were the re s of regulation of X chromosome function She tulated that in a given somatic cell of a female nmal only one of the two X chromosomes is active and that this is the result of inactivation of one X chromosome early in the development of the zygote She suggested that it is random whether the maternal or the paternal X chromosome becomes inactivated but that once the inactivation process has taken place the same X chromosome will be inactivated in all daughter cells of the original cell

In the years since Mary Lyon published the first paper on her hypothesis in 1961 confirmatory evi dence has come from many studies Today this biological phenomenon may well be referred to as the *Lyon principle* rather than the *Lyon hypothesis* Early and important evidence for the validity of this concept in man originated from studies on females who were heterozygous for G6PD deficiency In such heterozygotes two populations of red blood cells were demonstrated one possessing and one lacking G6PD activity as predicted by Mary Lyon s hypothesis Also cell clones established from skin biopsies of females heterozygous for electrophoret ic variants of G6PD turned out to have characteris tics different from mass culture cells Both G6PD alleles were expressed in the latter whereas the product of only one allele could be demonstrated in the clones This showed that only one of the X linked alleles was active in the cell from which the clone originated and also that the pattern of X chromosome inactivation had persisted through cell divisions This was a direct confirmation of Lyon s prediction that once the inactivation phenomenon had taken place it would always be the same X chromosome which was inactivated in all the prog eny of that cell

In the years since these important experiments were conducted similar studies have been made on the behaviour of other X linked enzymes Thus two cell populations have been found in hetero- zygotes for hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency phosphoglycerate kinase variants α galactosidase deficiency and phosphorylase B kinase deficiency Also het erozygotes for Hunter s disease exhibit two cell

populations with respect to cellular mucopolysaccharide accumulation

The cytological expression of the inactivated X chromosome is the sex chromatin body or the Barr body which is present in the nucleus of cells from females Only one X chromosome is active even in individuals with more than two X chromosomes In *these individuals the number of Barr bodies will be* the number of X chromosomes minus one

Whereas the paternal and maternal X chromosomes have an equal chance of becoming inactivated in cells with a normal karyotype cells with structural X chromosome anomalies behave distinctly different Thus human cells with X chromosome deletions exhibit inactivation of the abnormal X chromosome In non reciprocal translocations in humans the rearranged X chromosome is the one which becomes inactivated

Both X chromosomes are active in oocytes It appears that two active X chromosomes are necessary for normal meiosis Females with Turner s syndrome who have only one X chromosome (karyotype XO) are sterile two functional X chromosomes seem to be necessary for normal de*velopment of the ovaries There is evidence that for* normal spermatogenesis in males the X chromosome needs to become heterochromatic

It was originally thought that the whole X chromosome is subject to inactivation Elegant studies of women who were heterozygous at more than one X linked locus have supported this view

the linkage phase is known in such women predictions can be made concerning the of both enzymes in individual cells or cell if the genes for two enzyme deficiencies are coupling (on the same member of the X chromosome pair) a given cell would exhibit neither or both enzyme activities Such studies have shown that two enzyme loci on the same X chromosome are either both active or both inactive as predicted by the original hypothesis Nevertheless it is not clear that every X linked locus is inactive Thus there is some evidence that the locus for the Xg blood group system is not inactivated heterozygotes appear to have one red cell population only However, this would not necessarily mean that both Xg loci are active in heterozygotes Very little is known about the *biochemistry of the Xg(a) anti*gen Hypothetically it could even become adsorbed to the red cells following synthesis by other cells

The exact timing of the inactivation event is n known *However studies in the mouse have r* vealed differences in fluorescence between the tw X chromosomes in embryos with more than 40 ce (early blastula stage) but not earlier This proble has also been approached by studies of enzym controlled by X linked genes in early mouse e bryos The expectation would be that inactivatio of one X chromosome has taken place wheneve unimodal distribution of enzyme activity is ol served since the difference between male a female embryos before X chromosome inactivati should result in a bimodal distribution Su enzyme analyses conducted on mouse embry were in agreement with the results from cytologi studies There is now good evidence that the ina tivation in the mouse occurs between the mor and early blastocyte stages This evidence em nates from studies on the activity of the X link enzyme HGPRT (2 5)

From a functional point of view the inactivatio of one of the X chromosomes in somatic cells females effectively causes a mosaic condition heterozygotes for deficiencies of X linked enzyme *The X linked enzyme will be present in one c* population but not in the other Since it is rand which one of the two X chromosomes becom inactivated the fraction of cells in which the chromosome with the gene specifying the norm enzyme is active may occasionally be very high very low This has consequences of clinical impo tance Thus females who are heterozygous f hemophilia A exhibit a wide spectrum of coagul tion factor VIII concentrations and the levels w be within normal limits if by chance there are ma cells which have the X chromosome carrying t gene for normal factor VIII as the active one Th there are good biological reasons for the difficult in detecting a significant fraction of carriers of linked disorders This is true not only for the dete tion of carriers of hemophilia but also for attem to detect the carrier state for the Duchenne type muscular dystrophy by means of creatine kina activity determination

The opposite extreme of normal coagulation fa tor VIII levels is the occasional manifestation clinical hemophilia in heterozygous females Th *Holmberg et al (4) reported on a woman who h* clinically manifest hemophilia B but was heterozygote This was definitely proven by t fact that she had given birth to a healthy boy with

normal masculine karyotype Since his only X chromosome came from the mother she must have had the gene for normal coagulation factor VIII on one of her X chromosomes Before the event of the Lyon principle a reasonable interpretation of the occurrence of a chromosomally normal female with hemophilia would be that of heterozygosity in combination with a new mutation (provided that the father of the woman was healthy)

In this issue Hamers et al (3) report studies on a kindred with Fabry s disease In this X linked disorder α galactosidase activity is significantly reduced and the clinical picture is dominated by pain and skin lesions and renal failure at later stages The patients lack the A isoenzyme of α galactosidase and there is an accumulation of ceramide trihexoside in blood vessels the nervous system kidneys cornea and other tissues

The manifestations of Fabry s disease in heterozygous females represent an excellent clinical illustration of the fundamental biological phenomenon of Lyonization Depending on the number of cells which have the X chromosome with the normal gene inactivated the clinical manifestations vary greatly Thus not all heterozygotes among the patients of Hamers et al had pain or skin lesions whereas others were severely affected Interestingly the clinical manifestations did not necessarily reflect the enzyme level as detected by the methods used Clearly the manifestations in heterozygous females are modified by other factors hereditary or environmental A given gene operates within the total genotype of the individual and the genetically determined biochemical reactions may be influenced by environmental and nutritional factors As so often in clinical medicine we may be faced with a situation where we must consider heredity *and* environment not only one to the exclusion of the other

An important finding in the kindred studied by Hamers et al was that of dissimilar α galactosidase A expression in monozygotic twins This argues strongly against the possibility that X chromosome inactivation should be non random in heterozygotes for this disease as had been suggested

In X linked nephrogenic diabetes insipidus a partial defect is also demonstrable in females The varying manifestations in such females suggest that in this disorder as well the phenomenon of X chromosome inactivation may be a cause for clinical variation Several other cases of varying clinical manifestations in females probably caused by Lyonization could be listed However the above examples may suffice to illustrate the need to be aware of X chromosome inactivation for the understanding of variability in clinical manifestations and of the problems inherent in attempts to detect female carriers of X linked disorders

The insight into regulation of X chromosome function which has followed in the years since the Lyon principle was first formulated has made possible several new approaches in medical research Linder and Gartler (6) could demonstrate that uterine myomas originate from one single cell by examining X linked enzymes in such material from heterozygous females A similar approach whereby cellular monotypy was found formed the basis for Benditt s hypothesis (1) that atherosclerotic lesions originate from one single parent cell Data which appear to confirm this finding have been published pointing to a genetic event in a somatic cell as an important cause for such lesions Thus clinical as well as experimental medicine has benefitted significantly from the work on X chromosome inactivation in mammals which was started a mere 20 years ago

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Tumors of the parathyroid glands Atlas of tumor pathology 2nd series no 14 By Benjamin Castleman and Sanford I Roth 96 pages US $4 50 Armed Forces Institute of Pathology Bethesda Maryland 1978

This volume is the last in the excellent series of monographs treating different problems in tumor pathology They are all of great interest not only to the professional anatomo-pathologists but also contain excellent information regarding recent developments in clinical problems relevant to the subject The readers of the Acta Medica Scandinavica will find interesting facts about such problems as clicinal symptoms and epidemiology of hyperparathyroidism beside an atlas of both macro- and microscopical anatomy

Castleman is without doubt the leading pathologist in this subject and the experience from Massachusetts General Hospital is unique both as regards metabolic surgical and pathological aspects of the disease The book is profusely illustrated and the pictures are of very high quality It seems to me that this must be a real goldmine for many specialists who are interested in the field from different points of view

Of special importance is the discussion about the different types of functional hyperparathyroidism This problem has been clearly delineated by Castleman in pathology and by the clinicians in Boston It seems clear that adenoma located in one gland is the cause in about 80% of the patients whereas hyperplasia occurs in practically all the others with about 15% chief cell hyperplasia and about 1–2% hyperplasia of the clear cells Carcinoma is quite less than 3% The clinical anatomical findings in erent processes are treated and it is evident that independent of each other The facts seem to the assumption that carcinoma does not arise from enoma

Jan G Waldenstrom

Current problems in cancer vol III no 5 Plasma cell neoplasms By Raymond Alexanian 60 pages $5 00 Year Book Medical Publishers Chicago and London 1978

During the last years some new series treating current problems and topics in haematology or oncology have been started It is clear that the frontiers are advancing rapidly in both sciences and it is also evident that they are closely connected Nobody can contradict the statement that a first rate modern oncologist has to be well versed in haematology to a certain extent this is also true mutatis mutandis

The series regarding cancer problems contains an lent very short monograph by Alexanian who has de his research chiefly to the treatment of multiple my and related problems There is also a list of current that will be treated in forthcoming issues This list tains a number of important and interesting subje seems to me that this type of information in oncolog the Year Book Publishers and with an editorial board leading departments of oncology may be of great in also to the internists It is evident that oncology w come of ever increasing importance to internal me and this small monograph on the plasma cell neopla very well suited for internists

About half the part on myeloma treats the thera this condition and the other half contains an adm concentrated presentation of the most important dia tic facts It is always a pleasure to follow an autho has a real personal experience in the field that he scribing Even if the reviewer does not agree on all regarding the treatment system used by Alexania presentation makes very stimulating reading and is well organized

Also other plasma cell dyscrasias and gammap including Waldenström s macroglobulinemia are ver presented

Jan G Waldenstr

British Medical Bulletin The HLA System vol 3 3 Edited by W F Bodmer 320 pages £5 or $ Published by The Medical Department The B Council 65 Davies Street London W1Y 2AA 1978

This volume of the British Medical Bulletin gives a h up-to-date survey of the major human histocompati system or complex—the HLA system as defined by of closely linked loci on chromosome no 6 Contrib to this issue are practically all the best known HL search people in the United Kingdom

The volume covers more or less all aspects of the system including serological and cellular typing ir tance in relation to transplantation and the associ between the HLA system and various diseases genetics and chemistry of the HLA system and th tigens are also covered as are other genetic markers or less closely linked to the old' HLA A and B

The volume can be highly recommended for every interested in the HLA system clinicians as well as specialised people working with tissue typing The e Walter Bodmer has as expected secured individual tributions with a high scientific quality

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Relationship Between Biochemical and Clinical Features in an English Anderson-Fabry Family

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TRACT The relationship between biochemical arameters and clinical symptoms in angiokeratoma orporis diffusum universale (Anderson Fabry s dis-) has been studied in an extensive English family biochemical parameters measured were α lactosidase activity in urine and in single hair and the urinary glycosphingolipid excretion 24 h The clinical symptoms evaluated included occurrence of pain, the prevalence of skin le sions an abnormal ECG cornea verticillata and other features Nine male patients and 13 female carriers were studied No correlation between bio-chemical parameters and the severity of the clinical symptoms could be found either in the hemizygotes or in the heterozygotes The urinary α galactosidase activity in all the heterozygotes lay within the normal range All the obligate heterozygotes (mothers and daughters of hemizygotes) could be detected by lysis of hair roots Additional heterozygotes were recognized on the basis of clinical symptoms and hair root analysis

Key words Fabry s disease lyonisation heterozygote detection α galactosidase

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Anderson Fabry s disease or angiokeratoma corporis diffusum universale is an inherited metabolic disorder of glycosphingolipid metabolism (30) caused by deficiency of the lysosomal enzyme ceramidetrihexosidase (EC 3 2 1 47) an α galactosidase (17 27) Whereas two α galactosidase isoenzymes A and B are present in normal tissue the former is absent in Fabry s disease (4 23) The latter enzyme has recently been identified as N acetyl-α galactosaminidase which has some activity towards substrates containing a terminal α galactosidic moiety (7 28) Thus the B isoenzyme has no relation to Anderson Fabry s disease

The enzymic defect in Anderson Fabry s disease results in progressive accumulation of galactosyl (α 1→4) galactosyl (β 1→4) glucosylceramide (ceramidetrihexoside or ceramide 3 abbreviated as CTH or GL 3) in most tissues of the body especially in kidney (26) and the cardiovascular system (6) but also in liver (26 31) spleen (26 31) pancreas (26) and ganglion cells of the peripheral nervous system (26) Increased concentrations of GL 3 are also found in urinary sediment (8 31) and plasma (5 33) A second glycosphingolipid galactosyl (α 1→4) galactosylceramide (digalactosylceramide or ceramide 2b abbreviated as GL 2b) is found in elevated concentrations in kidney (31) urinary sediment (8 31) and pancreas (26)

The clinical features are of various kinds (18 31 35) In the skin there are numerous small very dark red punctate or hemispherical papules which are sometimes a few mm in diameter but often so small as to be difficult to detect The skin lesions may be one of the earliest manifestations and may lead to diagnosis in childhood Another typical feature is the intermittent pain in the extremities which is often induced by changes in environmental temperature Progressive accumulation of glycolipids in the kidneys results in renal impairment with gradual deterioration of renal function resulting commonly in death at the ages of 30–60 As a consequence of the systemic vascular involvement tortuous retinal

Abbreviations GL 3=ceramidetrihexoside GL-2b=digalactosylceramide or cross reacting immunological cardiogram

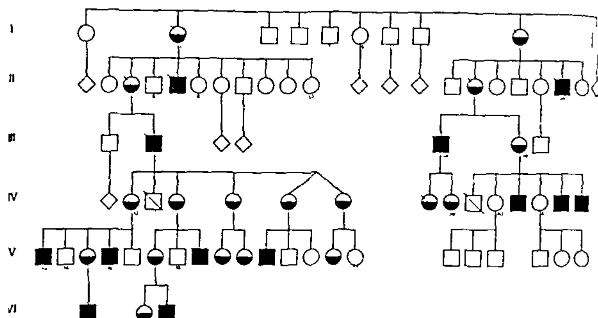


Fig 1 Pedigree of the family ◓ = Heterozygote ■ = hemizygote \ = deceased ◇ = unaffected offspring

veins are a common feature Cornea verticillata is also present in most affected adults Other features of the disease include oedema colitis cerebral vascular disturbances in early adult life cardiac enlargement and ECG abnormalities with or without hypertension aortic valve disease arthritis var veins necrosis of the head of the femur nails and pale nail beds

deficiency of α galactosidase A is inherited X linked fashion (14 15 20 35) Thus the male patients are hemizygotes and the mothers and daughters of the male patients are obligate heterozygotes In females heterozygous for the Fabry trait the amount of α galactosidase activity *in the somatic cells will depend on whether the* normal or the affected X-chromosome is expressed in these cells the other X chromosome being inactivated (19) The inactivation of one of the X chromosomes in the somatic cells of females (lyonisation) occurs in a random way in an early stage of embryonic development (19) Ropers et al (25) in contrast suggest that inactivation of the X chromosome in heterozygotes for the Anderson Fabry trait is not a random process but is influenced by the genotype However we have found that the expression of α galactosidase A differs in monozygous twins (IV-17 and IV 19) in the English family and in a Dutch family (22) this shows that the inactivation is not affected by the genoty Whereas in the hemizygotes α-galactosidase acti ty is absent in the heterozygotes a broad spectr of activities is found (9) The question arises of the relationship between the amount enzyme activity present in an individual amount of glycosphingolipids accumulated and severity of the clinical symptoms However measurement of the amount of α galactosidase a tivity in biopsies from heterozygotes can be m leading as intermingling of cells positive or negat for α galactosidase A no longer occurs after lyo sation has taken place at a certain stage of tiss development This causes the formation of patc *of cells of clonal origin (11 12) Consequently c* lular material of heterozygotes may consist entir of normal (or defective) cells depending on the si of the biopsy in relation to the size of the patch To circumvent this drawback the relationship b tween urinary α galactosidase activity and t amount of urinary glycosphingolipids was studie because the enzyme activity as well as the g cosphingolipids in urine are derived mainly fr the kidneys (3 8) Another possibility to circu vent the above problem is the use of cellular mate al derived from a source with a known number primordial cells and a known size of the patch This is the case with hair roots which origina

om only a few cells at the time of lyonisation and rm patches on the scalp of about 0 004–0 021 mm² — 2)

In this paper the relationship between the level f α galactosidase A activity the amount of gly osphingolipids excreted in the urine and the verity of the clinical symptoms was investigated i hemizygotes and heterozygotes in a single Eng sh Anderson Fabry family α Galactosidase ac vity was measured in urine and in single hair roots lucked from different areas of the scalp

SUBJECTS AND METHODS

All persons studied were members of a single extensive Anderson Fabry family (Fig 1) first described by John ton et al (16) whose original code has been maintained he deceased patients (I 2 I 9 II 5 II 7 II 32 II 36 II 12 and III 38) have been described by Johnston et al None of the individuals studied had renal failure

Collection of 24-hour urine was started in the morning n plastic bottles without any preservatives The next morning the urines were collected and centrifuged for 30 min at 22 000×*g* within 6 hours after collection The sedi ment was freeze-dried and stored at −20°C until further use Portions of 100 ml of the supernatant were processed and the ratio of β hexosaminidase to α-galactosidase was determined exactly as described by Rietra et al (24) The whole supernatant from patients IV-41 and V 13 was processed and used for detecting whether cross reacting immunological material (CRIM) was present exactly according to Rietra et al (23) The freeze-dried urinary sediments were processed essentially as described by Vance and Sweeley (34) and GL 3 and GL 2b were measured gaschromatographically according to the method of Sweeley and Tao (32) Less than 24-hour urine portions were obtained from some of the children In such cases a semiquantitative glycosphingolipid analysis was carried out using thin layer chromatography according to Vance and Sweeley (34) With this method no glycosphingolipids can be detected in 100-ml portion of urine from a healthy control

Hair roots plucked by hand from different areas of the scalp were classified as normal heterozygous or hemizygous (9) Total α galactosidase and β hexosaminidase activities were measured as described by Ejiofor et al (9)

The severity of pain was expressed in categories varying from absent ( ) to very severe (+++) The other clinical features were evaluated as absent (−) or present (+)

RESULTS AND DISCUSSION

The results of the investigations are listed in Table I

Hemizygotes Patient V 16 now lives in Denmark His hair roots were collected in Denmark by Dr F Svendstrup transported by air to London and assayed there No other biochemical parameters were measured in this patient From patients VI 1 and VI 3 who were too young for 24-hour urine to be collected without special equipment very small samples were collected just enough to measure the urinary enzyme ratio for diagnosis From patient VI 3 it was impossible to collect hair roots because the hairs were too fragile to pull out the roots

The urinary ratio β hexosaminidase/α galactosidase in all the hemizygotes was >40 as expected All the hair roots could be classified as hemizygous or occasionally as heterozygous Table I clearly shows that the clinical symptoms in the hemizygotes are variable even among patients of similar age The same conclusion was drawn by Van den Bergh (2) in a study of the clinical symptoms of 50 hemizygotes described in the literature Because all hemizygotes studied here belong to one and the same family they must have the same genotype for α galactosidase A thus the variability of the clinical symptoms must be explained in terms of the rest of the genotype and/or environmental factors Another parameter that can be measured more accurately than the clinical symptoms is the glycosphingolipid excretion but again a variability is found which is related neither to age nor to the clinical features

Obligate heterozygotes Although the urinary β hexosaminidase/α galactosidase ratio lay within the normal range (<20) the subjects could all be classified as heterozygotes on the basis of the hair root analyses a large number of which showed hemizygous values (9)

Other heterozygotes An additional number of subjects who are not obligate heterozygotes were also detected by means of the hair root analysis

In the heterozygotes too there does not always seem to be a clear correlation between the biochemical parameters and the clinical symptoms For instance patient III 39 has a reasonable amount of α galactosidase as may be concluded from the large proportion of normal hair roots and excretes indeed very little GL-3 and GL 2b but shows nevertheless clear clinical symptoms On the other hand patients IV 10 IV 19 and V 22 all show increased GL 3 and GL 2b excretion as well as clinical symptoms findings that may be correlated with the fact that they have low α galactosidase activity to judge from the large proportion of hemizygous hair roots Patient V 18 has the highest excretion of

Table I *Biochemical parameters and clinical symptoms in members of an Anderson Fabry famil*

N = normal Het = heterozygous Hem = hemizygous classified on the basis of the α-galactosidase activity in relat[ion to] the β-hexosaminidase activity N D = not determined

Subject	Age (y)	Urinary ratio β-hexosaminidase/α-galactosidase[a]	No of hair roots classified as				Glycosphingolipids in urinary sediment (μmol/24-h urine)		Clinical features				
			N	Het	Hem	Total	GL 3[b]	GL 2b[c]	Pain	Skin lesions	Abnormal ECG	Cornea verticillata	Other
Hemizygotes													
IV-41	38	40	0	0	17	17	0 918	0 268	+	+	+	+	Angina phl[…]
IV-43	29	93	0	0	10	10	1.248	0 122	+	+	–	+	Diffuse lu[…]
IV-44	20	63	0	0	16	16	2 519	0 453	+	+	–	+	
V 13	32	160	0	0	10	10	0 791	0 169	+++	+	–	+	Slow growth 160 cm Fe[…] fingers oed[…]
V 16	25	N D	0	0	6	6	N D	N D	+++	+	–	+	
V 20	17	1 0	0	2	9	11	0 954	0 241	++	+	–	+	Slow growth
V 23	15	79	0	2	8	10	0 941	0 024	+	+	–	+	Haematuria
VI 1	2	97	0	0	4	4	N D	N D	–	–	–	N D	
VI 3	1	127	N D				N D	N D	N D	+	N D	N D	
Obligate heterozygotes													
III 39	66	9 0	11	3	2	16	0 051	0 013	+	–	–	+	
IV 10	53	8 3	0	8	8	16	0 155	0 056	+	+	+	+	
IV 13	43	8.5	1	5	5	11	0 098	0 016	+	+	+	+	
IV 15	38	7 7	2	7	4	13	0 050	0 016	–	–	–	–	Tortuous ret[…] veins
IV 17	36	7 6	8	2	1	11	0 020	Trace	–	–	–	–	
IV 19	36	11	1	4	9	14	0 145	0 037	–	+	–	+	
IV 38	44	16	2	3	12	17	0 022	Trace	++	–	+	+	Fever nodul[…] vasculitis proteinuria oedema
V 15	28	2 7	1	5	3	9	0 044	Trace	+	–	–	N D	
	22	14	5	3	3	11	0 270	0 084	–	+	–	+	
[…]erozygotes													
	21	4 8	5	5	6	16	0 082	Trace	–	+	–	–	
	19	13	2	4	9	15	0 110	Trace	++	+	–	+	
	9	5 7	4	6	6	16	0 032	Trace	–	–	–	–	
[…]1 2	3	6 4	7	4	3	14	Present[d]		–	–	–	–	
Other family members													
V 24 (♂)	13	5.5	N D				Not detectable		–	–	N D	–	
V 25 (♀)	11	6 8	9	0	0	9	Not detectable[f]		–	–	N D	–	
V 27 (♀)	8	6.2	8	3	0	11	0 022	Trace	–	–	N D	–	

[a] <20 in normal individuals >40 in hemizygotes (22)
[b] Mean value in normal individuals is 0 025 and the range reported for hemizygotes is 0 120–4 91 (2)
[c] Trace amounts are found in normal individuals and trace amounts up to 0 86 μmol/24-h urine in Fabry hemizygotes
[d] Detected in thin-layer chromatograms of material from 70 ml and 137 ml urine
[e] Thin-layer chromatogram of material from 130 ml urine
[f] Thin-layer chromatograms of material from 84 ml and 120 ml urine

GL 3 and GL 2b found among the heterozygotes although from the hair root analysis it seems that she has an intermediate α-galactosidase activity Even more surprising is the observation in patient IV-38 who has a large proportion of defective hair roots and much pain but excretes very little if a[ny] GL 3 or GL 2b In contrast patient IV 17 h[as a] very large proportion of normal hair roots no cli[ni-]cal symptoms and no abnormal glycosphing[olipid] excretion The latter finding has been reported b[…]

fore (1 21) The opposite type of carrier with very low α galactosidase activity as indicated by analysis of urine plasma and leukocytes has been reported by Rietra et al (22) (carrier M K whose urinary β hexosaminidase/α-galactosidase ratio was ≥100) We were able to perform a glycosphingolipid analysis of 24-hour urine from this carrier the amount of GL 3 excreted per 24 hours was 1 79 μmoles and that of GL 2b 0 66 μmoles Thus the amount of glycosphingolipids excreted by M K is comparable to that excreted by hemizygotes Moreover M K has severe clinical symptoms (W P de Groot personal communication) Thus there seems to be a good correlation between the expression of α galactosidase A and the other parameters in this case

Three other family members The boy (V 24) could be diagnosed as normal and neither of the girls (V 25 and V 27) could be diagnosed as heterozygotes

Another conclusion that can be drawn from these results is that although determination of the urinary enzyme ratio is a good method of diagnosing hemizygotes especially if they are babies and have no clinical symptoms the diagnosis of heterozygotes by this method is not always possible owing to the wide range of normal ratios Indeed the urinary β hexosaminidase/α galactosidase ratios in all of the heterozygotes in this English family lay within the normal range (Table I) Much less overlap between the distribution of α galactosidase activity in normal persons and Fabry heterozygotes is found in the α galactosidase levels in hair roots (9 13 29) and this is a very good method for diagnosis of heterozygotes However the combination of the hair root analysis with the measurement of glycosphingolipid excretion and the clinical diagnosis is the most reliable method

The general conclusion of this study is that there is no clear correlation between the expression of α galactosidase A (i e the amount of α galactosidase activity present) and the biochemical or clinical features with the possible exception of the very mildly and severely affected carriers Obviously other factors such as the complete genotype of the subject play an important role in determining the expression of the clinical symptoms and the course of the disease Furthermore as a consequence of the lyonisation phenomenon it is impossible to prove conclusively that a female member of a Fabry family who has a heterozygous mother is not heterozygous herself It is in theory possible that inactivation of one of the X-chromosomes has occurred in such a way that the unaffected X-chromosome is expressed in all somatic cells so that the α galactosidase activity is completely normal Thus since it is difficult if not at present impossible to establish with absolute certainty that a female member of an Anderson Fabry family is not heterozygous for the trait all pregnancies in the family must be considered at risk However prenatal diagnosis of Anderson Fabry s disease is possible (5 10)

Finally it should be noted that no CRIM could be detected in the urine of two hemizygotes from the English family (IV 41 and V 13) The absence of CRIM has also been established in two American patients (4) in a Dutch (23) an Italian an Irish and a French patient (Hamers unpublished observations) Thus there is no indication as yet of genetic heterogeneity in Anderson Fabry s disease

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T_4, T_3 and Reverse-T_3 Determinations in Connection with the TRH test in the Evaluation of Possible Hyperthyroidism

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ABSTRACT One disadvantage of the TRH test is that an absent or blunted TSH response is seen not only in hyperthyroid patients but also in some normal subjects The aim of the present study was to elucidate whether the discriminatory power between eu and hyperthyroidism could be increased by determining the T_3 and T_4 levels before and after the TRH administration The study population consists of 30 patients referred for evaluation of suspected hyperthyroidism The results show that all but one of the patients ($n=20$) who had T_3 levels within the normal reference limits increased these levels after TRH administration, whether their TSH response was normal or blunted One patient's T_3 levels decreased after TRH A the patients ($n=10$) who had T_3 levels within the hyperthyroid range showed a decrease after TRH The decrease was significantly correlated ($r=0$ 90) to the magnitude of the increase No consistent T_4 and no change in reverse T_3 response was obtained The addition of T_3 T_4 or reverse-T_3 determinations in connection with the TRH test does not seem to increase the discriminatory power of the test

Key words thyroxine triiodothyronine reverse triiodothyronine TRH test hyperthyroidism

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The recent development of radioimmunoassay techniques for the estimation of thyroid hormones and thyroid stimulating hormone (TSH) has provided a sufficiently sensitive and simple means of directly quantitating these substances in the serum in both normal and pathological states

The clinical value of TSH determinations is now well recognized in the diagnosis of primary hypothyroidism (7) In fact the discriminatory power of TSH determination is so good that a normal TSH level excludes primary hypothyroidism In the laboratory discrimination between eu and hyperthyroidism the determination of 3 5 3 triiodothyronine (T_3) seems to be superior to thyroxine (T_4) determination even when corrections are made for variations in the hormone binding serum proteins (8 14) The discriminatory power of T_3 determinations is also higher than the thyrotropin releasing hormone (TRH) test even though a normal TSH response to TRH stimulation excludes hyperthyroidism (13) One disadvantage of the TRH test is that an absent or blunted TSH response is seen not only in hyperthyroid patients but also in some normal subjects (9 14) The reason for an absent or blunted response in normal individuals is unclear

It has recently been claimed that determination of T_3 and T_4 levels is of value as a complement to the TRH test (1 2 4 11) The aim of the present investigation was to elucidate whether the discriminatory power of the TRH test could be increased by the additional determinations of T_3 reverse T_3 (3 3 5 triiodothyronine) and T_4 levels Special reference was made to euthyroid subjects demonstrating an abolished or blunted TSH response An increase in T_3 or T_4 levels despite an absent or blunted TSH response may be found if the sensitivity of the assay methods is higher for T_3 and T_4 than for TSH

PATIENTS AND METHODS

Thirty patients referred for evaluation os suspect hyperthyroidism were included in the study Five were men with a mean age (±S D) of 44±10 years (range 29–54)

Abbreviations TSH = thyroid stimulating hormone TRH = thyrotropin releasing hormone T_3 = 3 5 3 triiodothyronine reverse T_3 = 3 3 5 triiodothyronine T_4 = thyroxine

Table I *Serum levels of T_4, T_3 and reverse T_3 in the three groups*

	Group 1			Group 2			Group 3		
	0	120	180	0	120	180	0	120	180
T_4									
m	76 6	85 6	86 9	173 5	169 0	176 3	86 9	91 3	89 3
±S E	5 8	6 6	6 5	17 0	17 0	17 6	8 2	8 6	7 7
p		*			N S	N S		N S	N S
T_3									
m	1 75	2 23	2 04	4 82	4 12	4 07	1 93	2 15	2 14
±S E	0 14	0 14	0 15	0 65	0 50	0 46	0 11	0 09	0 18
p		**	***		***	**		**	N S
Reverse T_3									
m	0 20	0 23	0 22	1 38	1 40	1 38	0 35	0 31	0 32
±S E	0 03	0 02	0 02	0 34	0 39	0 37	0 06	0 04	0 05
p		N S	N S		N S	N S		N S	N S

N S = Not significant *0 01<p<0 05 **0 001 <p<0 01 ***p<0 001

The mean age (±S D) of the women was 56±14 years (range 21–76) Each patient underwent a full clinical investigation Thyroid function tests included estimation of T_4, T_3, reverse T_3 and *TSH* levels as well as the *TRH* test T_4 suppression test and scintiscans

T_4 and T_3 were determined by radioimmunoassay as previously described (10) The reference value in serum (mean ± S D) for T_4 is 89±17 for T_3 1 77±0 34 nmol/l

Reverse T_3 was determined using a commercially available kit (Hypolab Coinsins Switzerland) The normal serum level (mean±S D) is 0 34±0 20 nmol/l

Serum TSH was determined with a commercial kit ebas TSH test Pharmacia Diagnostics Uppsala) The reference limit for men is <7 2 and for <5 5 μU/ml

TRH test was performed on an out patient basis .00 μg synthetic TRH (Hoffman La Roche Basel zerland) administered intravenously Serum samples were drawn before and at 20 and 60 after the injection for TSH analysis and at 120 and 180 after the injection for TSH T_4 and T_3 and reverse T_3 determinations A TSH increment of more than 3 0 μU/ml during the first hour is regarded as a normal response (14)

The T_4 suppression test and scintiscans were performed according to standard procedures (16) Three mg of *l* thyroxine was given orally as a single dose

RESULTS

The results of the complete clinical and laboratory evaluation showed that the patients could be divided into three groups *Group 1* comprised 10 patients with total evidence of normal thyroid function *Group 2* comprised 10 patients with total evidence of hyperthyroidism *Group 3* comprised 10 patients in whom a definite diagnosis of a disease of thyroid function could not be made by the clini investigation alone and in whom the basal T_3 verse T_3 and T_4 levels were within the referer interval despite an impaired TSH response to TR

Group 1 Eight of the 10 patients in this gro were women The age range was 23–65 years (me 43 6) All were clinically euthyroid All basal T_4 and reverse T_3 levels were within the referer limit (mean ± 2 S D) and the TSH response to TI was normal (increment > 3 0 μU/ml) in all s jects The TSH increment was 8 28±1 71 μU/ (mean ± S E) The results are shown in Table I

All patients showed increased levels of T_3 af TRH A highly significant (p<0 001) increase in levels was obtained after both 120 28 8% a 180 16 9% in the whole group No signific change was observed in reverse T_3 levels af TRH

Eight patients showed increased levels of T_4 af TRH decreased values were seen in two (–. nmol/l in both) A significant increase in T_4 lev was obtained in the whole group both after 12 12 8% (0 01<p<0 05) and after 180 14 7 (0 001 <p<0 01)

Thus in this group of patients with apparen normal thyroid function and normal TSH respon to TRH an increase in T_3 was obtained in all p tients after 120 and 180 Only 8 of the 10 patier also showed an increase in T_4 levels No change reverse T_3 was seen

Group 2 Eight of the 10 patients in this gro were women The age range was 46–73 years (me

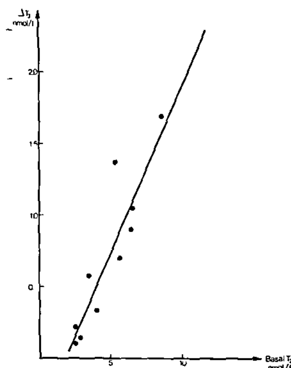


Fig 1 Decrease in T_3 levels after TRH administration in the hyperthyroid patients (group 2)

59 6) All had clinical signs and symptoms of hyperthyroidism All basal T_4 and T_3 levels and all but two reverse T_3 values were within the hyperthyroid range All patients had an abolished TSH response to TRH The results are shown in Table I

All patients showed decreased T_3 levels after TRH A significant decrease in T_3 levels for the whole group was obtained after 120 13 0% ($p<0$ 001) and after 180 13 3% (0 001$<p<$0 01) The decrease was significantly correlated to the basal T_3 levels ($r=0$ 90) as shown in Fig 1

No significant changes in reverse T_3 or T_4 levels were obtained in this group

Thus in this group of hyperthyroid patients a decrease in T_3 levels was obtained in all patients both after 120 and after 180 No significant change in reverse T_3 or T_4 levels was seen

Group 3 Nine of the 10 patients in this group were women The age range was 45–76 years (mean 60 2) The state of the thyroid function could not be settled by the clinical examination alone All basal T_3 reverse T_3 and T_4 levels were within the reference limit (±2 S D) Three of the patients had an abolished TSH response to TRH the response in seven was blunted (0 <increment <3 0 μU/m The results are shown in Table I

Four of the 10 patients had a normal radioiodi uptake test and a normal T_4 suppression test T scintiscans revealed no autonomously functioni nodule thus fulfilling our criteria for a normal th roid function All four patients showed increas levels of T_3 after TRH The mean increase w 15 9% at 120 and 22 1% at 180 No consistent response was obtained

Another four of the 10 patients had abnormal suppression tests and scintiscans indicating au nomously functioning nodules Three patie showed increased levels of T_3 after TRH and c decreased level The mean increase was 25 8% 120 and 16 6% at 180 No consistent T_4 response was obtained

The remaining two patients had both been pre viously operated upon for toxic nodular goiters The 24 hour radioiodine uptake tests were 51 and 46% respectively For technical reasons no T_4 suppression test could be performed Both patients showed increased levels of T_3 after TRH No sig nificant change was seen in reverse T_3 levels after TRH

Thus the results show that all but one patient with normal basal levels of T_3 increase these levels after TRH administration despite blunted or abol ished TSH responses and autonomously function ing thyroid nodules

DISCUSSION

The present results indicate that patients with nor mal basal levels of T_3 significantly increase these levels 120 and 180 min after TRH administration regardless of a normal blunted or abolished TSH increase The increase in T_3 levels seen in normals is consistent with the findings of previous investiga tors (1 3 6 11 13 15) The observation of an increase in T_3 levels despite an abolished or blunted TSH response is both in accordance and in contrast to previous reports (5 12) Dige Pedersen and Hummer (5) found that the T_3 response to TRH was significantly correlated with the TSH increase both in normal subjects and in patients with non toxic goiter while Sawin and Hershman (12) reported that there was no correlation between the rise in serum TSH and T_3 levels The finding of an in crease in T_3 levels despite an abolished or blunted TSH increase might have to do with a low sensitivi

ity of the TSH assay technique However further studies with five different commercially available TSH radioimmunoassay kits generally used in clinical practice yielded similar TSH results (unpublished observation)

The present results also show that all patients with basal levels of T_3 within the hyperthyroid range demonstrate a reduction in these levels after TRH administration The decrease was significantly correlated to the magnitude of the basal level Similar findings do not seem to have been reported previously The mechanism behind the decrease is so far unknown The results thus indicate that the determination of T_3 levels as a complement to TSH determinations is of no major diagnostic value for the discrimination between eu and hyperthyroidism This conclusion can be drawn on the basis that an increase in T_3 levels was obtained in all patients with normal T_3 levels and a decrease was demonstrated in all patients with T_3 levels within the hyperthyroid range Thus the determination of the basal T_3 levels alone is sufficient The inconsistent T_4 response and the absent reverse-T_3 response indicate that the determination of these parameters is of no additional diagnostic value as a complement to the TRH test for discrimination between eu and hyperthyroidism

In conclusion the determination of T_3 reverse T_3 and T_4 levels in addition to the determination SH after TRH administration does not increase criminatory power of the TRH test in the y diagnosis of eu or hyperthyroidism

ACKNOWLEDGEMENTS

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Function of Pituitary-Thyroid Axis after Surgical Treatment of Non-Toxic Nodular Goitre

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ABSTRACT Fifty consecutive patients with benign euthyroid nodular goitre underwent goitre resection In uninodular goitres a remnant of normal thyroid tissue was left, while in multinodular goitres the remnant presented varying degrees of nodularity The pituitary thyroid function was determined before operation and 3, 6, and 12 months after surgical treatment by measuring serum T_4 serum T_3, FT_4 index, serum TSH and TSH response to TRH Moreover, determination of thyroid autoantibodies and ^{99m}Tc scintigraphy were carried out In the uninodular goitre group removal of a single hypofunctioning adenoma caused a slight but significant increase in thyrotrophic function without significant changes in serum levels of thyroid hormones The thyrotrophic function showed a more pronounced rise in the multinodular than in the uninodular goitre group Nonetheless a decrease in serum levels of thyroid hormones took place Numerically, the fall was modest, albeit significant Overt hypothyroidism developed in only one patient According to the present knowledge of development and maintenance of goitre, our results do not indicate that thyroid replacement therapy is required as a routine measure after nodular goitre resection Overt thyroid failure or abnormally high TSH levels—conditions in which thyroid substitution should be offered—developed only in the group operated upon for multinodular goitre

Key words non toxic goitre surgical treatment pituitary thyroid axis thyroid function

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Increased thyrotrophic function as the only biochemical abnormality has been described in a high percentage of patients treated surgically for non toxic goitre (6 9 11 14) Whether the finding reflects a state of subclinical hypothyroidism (5 22) indicative of thyroid substitution therapy as a routine measure (6 9 14) is still a matter of debate The present study deals with this problem as we have assessed the pituitary thyroid function at regular intervals in patients undergoing surgical treatment for non toxic goitre

PATIENTS AND METHODS

During a one year period a consecutive series of 50 patients with benign non toxic nodular goitre underwent goitre resection All patients were otherwise healthy admittedly euthyroid—clinically as well as biochemically—and received no hormonal medication The pituitary thyroid function and clinical status were assessed before operation and 3 6 and 12 months postsurgically

Laboratory investigation

The pituitary thyroid function was determined by measuring serum total thyroxine (T_4) serum total triiodothyronine (T_3) serum thyroid stimulating hormone (TSH) serum TSH response to thyrotrophin releasing hormone (TRH) and T_3-resin uptake Free T_4 index (FT_4I) was calculated by the formula serum $T_4 \times T_3$-resin uptake $\times 10^{-2}$ Autoantibodies including thyroid microsomal and colloid (CA 2) antibodies were measured by indirect immunofluorescent technique Thyroglobulin antibodies (CA 1) were estimated by the tanned red cell agglutination test (Laboratory of Immunology Statens Seruminstitut Copenhagen) Moreover a ^{99m}Tc pertechnetate scintigraphy of the thyroid gland was carried out using a gammacamera (Nuclear Chicago Pho/gamma HP 2) provided with a parallel hole and a pinhole collimator

Serum T_4 was measured by competitive protein binding technique (Tetrasorb Abbott) median 100 range 58–174 nmol/l and serum T_3 by a radioimmunoassay (Abbott) median 2 4 range 1 5–3 6 nmol/l T_3 resin uptake (Triosorb Abbott) values were expressed proportional in relative terms to a reference serum fixed at 100 median 98 range 67–129 FT_4I showed a median value of 99 range 59–169 Serum TSH was measured by a radioimmunoassay using the kit from Pharmacia Diagnostics The detection limit for TSH was 1 5 mU/l Normal values ranged from ≤ 1 5–6 0 median 2 0 mU/l

Abbreviations T_4=thyroxine T_3=triiodothyronine TSH=thyroid stimulating hormone TRH=thyrotrophin releasing hormone FT_4I=free T_4 index

Concerning the TRH test 200 μg of synthetic TRH (Hoechst) was rapidly injected intravenously between 9 a m and 11 a m Blood was sampled prior to (−5 and 0) and 20 30 40 and 60 min postinjection for determination of TSH Δ max TSH was defined as the difference between serum baseline TSH and serum peak TSH during the test In females peak TSH ranged from 5 4 to 20 0 median 10 1 mU/l and Δ max TSH from 3 9 to 17 0 median 7 5 mU/l In males peak TSH ranged from 4 7 to 8 2 median 6 8 mU/l and Δ max TSH from 2 6 to 5 9 median 4 3 mU/l

The reference values defined as median and range refer to results from 103 healthy individuals aged 21–70 years examined in our laboratory Ranges are indicated by the lowest and highest value measured

Statistics

Statistical analysis was performed using the Friedman test for paired data against time and the Mann Whitney test to compare results between groups $P<0\ 5$ was considered significant

Goitre specifications

In 18 patients (14 females 4 males age range 23–65 median 33 years) a solitary adenoma was removed In 32 patients (28 females 4 males age range 25–70 median 51 years) a multinodular goitre was resected bilaterally

In uninodular goitres the presence of a solitary adenoma was confirmed by surgery All nodules were hypofunctioning defined by decreased uptake of ^{99m}Tc A circumscribed defect was visualized on the scintigram corresponding to the palpable mass on the neck

In multinodular goitres the multinodularity was confirmed surgically On the scintigram ^{99m}Tc uptake was irregular with scattered non functioning areas correspond
to the goitrous regions
was indicated by persistence of obstructive
ns suspicion of malignancy or cosmetic reasons
from the series were patients with goitres
ng malignancy on histological examination and patients with uninodular goitres representing a hyperfunctioning autonomous adenoma The latter condition was *suspected on the initial scintigram by demonstration of a* hot nodule with partial or complete suppression of extranodular tissue and verified by T_3 suppression test (100 μg of T_3 daily for 7 days) followed by a TSH stimulation test (10 IU TSH intramuscularly) and repeated scans

The median duration of goitre was significantly longer in the multinodular (8 years) than in the uninodular group (1 year) The median weight of the removed thyroid specimens was also significantly higher in the multinodular group (55 g range 10–360) than in the uninodular group (15 g range 5–165) Lymphoid thyroiditis was not found in any specimen In 7 patients slightly elevated thyroid antibodies were demonstrated the microsomal type in 6 and CA 2 type in one

In uninodular goitres the remnant tissue was normal on gross examination whereas it showed varying degrees of nodularity in most instances in multinodular goitres In multinodular goitre it was intended to spare a thyroid remnant of near normal gland size but in some cases a subtotal resection was done

RESULTS

Pituitary thyroid function before operation

The preoperative values of serum T_4 FT_4I serum T_3 were significantly higher in the multinod lar than in the uninodular group In both grou however values were within normal limits significant difference in binding properties found between the groups Serum basal TSH le and serum peak TSH values during TRH test patients with multinodular goitre did not di significantly from those in patients with uninod goitre whereas Δ max TSH values were sign cantly lower in the multinodular group (Table I)

In uninodular goitre the TSH response (Δ m TSH) to TRH was impaired in 5 (28%) increased one and low normal in 12 patients In multinodu goitre the TSH response was blunted or decrea in 23 (72%) increased in one and normal i patients

Pituitary thyroid function after operation

In the uninodular goitre group serum T_4 FT_4I a serum T_3 determined 3 6 and 12 months a surgery did not differ significantly from preope tive levels T_3 resin uptake was unchanged Ba TSH values were significantly raised but within normal range The TSH response to TRH showe modest but significant increase (Table I)

In the multinodular goitre group serum T_4 serum T_3 decreased significantly Also FT_4I lowered but not significantly T_3 resin upt showed a significant rise indicating reduced ing capacity Basal TSH values were significar raised exceeding the upper normal limit in 5 tients (16%) The TSH responses to TRH showe highly significant increase (Table I)

After operation the significant difference thyroid hormone levels between the two grou disappeared whereas a definitely higher thy trophic function developed in the multinodular th in the uninodular group Besides blunted or i paired TSH response to TRH was not found af surgical treatment On the contrary a tendency abnormally high responses was apparent pr dominantly in the multinodular group 12/32 (38% versus 3/18 (17%)

During follow up only one patient treated f multinodular goitre presented with clinical a biochemical evidence of hypothyroidism At months after operation she was placed on thyr

able I *Effect of goitre resection on thyroid function in 18 patients with non toxic uninodular (U) and 3 atients with non toxic multinodular (M) goitre (median and range)*

		Before operation	Months after operation 3	6	12	p^b
erum T_4 (nmol/l)	U	*97* 78–148	*101* 81–127	99 80–137	*105* 75–134	>0 05
	M	117 61–159	98 19–137	108 62–143	107 62–133	<0 01
	p	<0 02	>0 05	>0 05	>0 05	
T_4I (arbitrary units)	U	96 77–124	100 72–137	98 81–134	111 68–142	>0 05
	M	108 58–170	98 17–126	101 59–143	105 62–149	>0 05
	p^a	<0 05	>0 05	>0 05	>0 05	
serum T_3 (nmol/l)	U	2 15 1 60–2 80	2 15 1 40–2 80	2 15 1 50–2 80	2 10 1 45–3 00	>0 05
	M	2 45 1 65–3 50	2 35 0 95–3 00	2 25 1 75–3 00	2 20 1 55–2 70	<0 01
	p^a	<0 02	>0 05	>0 05	>0 05	
serum TSH (mU/l)	U	≤1 5 ≤1 5–3 6	2 1 ≤1 5–6 1	2 3 ≤1 5–5 4	2 3 ≤1 5–6 1	<0 01
	M	≤1 5 ≤1 5–9 5	3 6 ≤1 5–9 9	3 2 ≤1 5–9 5	3 2 ≤1 5–11 0	<0 001
	p	>0 05	<0 01	<0 05	<0 02	
serum peak TSH (mU/l)	U	5 4 1 8–39	7 6 2 1–49	9 0 4 0–56	8 6 3 5–60	<0 01
	M	3 9 ≤1 5–49	17 5 5 2–55	15 2 2 8–76	15 7 4 3–45	<0 001
	p	>0 05	<0 001	<0 01	<0 01	
Δ max TSH (mU/l)	U	3 8 0 3–36	5 3 0 6–42	6 2 2 3–51	5 8 1 7–54	<0 01
	M	2 1 0–40	14 7 3 6–47	12 9 1 3–68	13 5 2 3–41	<0 001
	p	<0 05	<0 01	<0 01	<0 01	

[a] Mann Whitney test [b] Friedman test

substitution therapy and excluded from further examination The other patients remained euthyroid both clinically and biochemically (serum T_4 serum T_3 FT_4I) None developed recurrent goitre

DISCUSSION

Our study showed that 1) Removal of a single *hypofunctioning thyroid* adenoma leaving a remnant of normal tissue caused a slight increase in thyrotrophic function without significant change in serum levels of thyroid hormones Although the thyrotrophic function increased significantly basal TSH values did not rise beyond the upper normal limit in any patient of the group 2) In multinodular goitres having as a rule a nodular remnant the thyrotrophic function showed a more pronounced rise than that observed in uninodular goitres and basal TSH values might exceed the upper normal limit Nonetheless a decrease in thyroid hormone levels was recorded Numerically the fall was slight albeit significant except for FT_4I and only *one patient developed overt hypothyroidism*

In a recent study on surgical treatment of nodular goitre Gemsenjager (6) found no significant change in levels of thyroid hormones or thyrotrophic function in 18 patients with remnants of normal thyroid tissue On the other hand the thyrotrophic function

was significantly increased in 13 patients with remnants of goitrous tissue, whereas no change was observed in thyroid hormone levels In other studies (9 11 14) also dealing with surgical treatment of non toxic goitres approximately 30% of patients developed elevated serum baseline TSH as the only biochemical abnormality Especially subnormal levels of serum T_4 were not recorded In these studies the goitre specifications were sparse and the results were collected unsystematically Apparently a rise in thyrotrophic function is a general feature after goitre resection especially in the group with remnants consisting of goitrous tissue whereas development of overt hypothyroidism is a rare occurrence

It is well documented that the TSH response to TRH in non toxic goitres shows a heterogeneous pattern with a definite trend towards lack of response parallel with increasing nodularity of the thyroid gland (1 3 4 8 12 15 16 19) The fact that TSH responsiveness to TRH recovers after goitre resection without biochemical evidence of hypothyroidism lends support to the theory of increasing functional autonomy as a general trend in goitre evolution (2 8) In our study the TSH response pattern to TRH before and after surgery is in complete agreement with this point of view The fall in thyroid hormone levels after multinodular goitre resection to levels of the same order as those found in ...inodular goitre group is also in accordance ...the view of increased autonomy associated ...the development of multinodular goitres

...he rise in thyrotrophic function after goitre resection in otherwise euthyroid patients may be explained by factors related to reduction in the mass of functioning thyroids tissue as recently suggested by Tunbridge et al (21) and Wilkin et al (22) rather than by overt hypothyroidism requiring replacement therapy This point of view is supported in our investigation by the fact that no progressive deterioration in thyroid parameters took place except in one patient during the period of observation irrespective of abnormally high thyrotrophic function

It is well recognized that goitre may recur after surgical treatment but it seems to be a minor problem based on low recurrence rates of 0–5% (10 13 17 20) Factors responsible for recurrence of goitre are not well known However a raised thyrotrophic function may be contributory Pickardt et al (18) and Gemsenjager et al (7) found a significantly higher incidence of elevated TSH reserve in p... tients with recurrent than untreated goitre But r... currence also occurred in several instances with increased thyrotrophic function Besides if recu... rence of goitre is solely TSH dependent a hig... rate than actually found should be expected in ... of the considerable number of patients with po... surgically elevated TSH levels

At present it is generally agreed that the ... velopment of non toxic goitre is TSH-dependent ... a compensation for impaired thyroid hormone p... duction On the other hand factors responsible ... the maintenance of goitre have not been clarifi... Therefore a rational basis for thyroid replacem... therapy after goitre resection still remains to ... defined However from a theoretical point of vi... conditions of overt hypothyroidism and/or abn... mally high baseline TSH values should be trea... with thyroid substitution

Accordingly our results do not indicate ... thyroid replacement therapy is required routi... following goitre resection Overt hypothyroidis... abnormally high TSH levels—conditions in wh... thyroid substitution should be offered—develo... only in the group operated upon for multinod... goitres

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Non-Selective and Selective β-1-Adrenoceptor Blocking Agents in the Treatment of Hyperthyroidism

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3STRACT Treatment for one month with proanolol or atenolol, a selective β-1 adrenoceptor ocking agent, was evaluated in 20 hyperthyroid pants The patients improved to the same extent on her drug, as shown by a clinical diagnostic index isal metabolic rate decreased by 11 % during both eatments while it was unchanged in seven un eated hyperthyroid controls Thyroxine concentra on did not change during any treatment During opranolol treatment T3 decreased from 4 6 to 3 9 nol/l while no changes were observed during enolol treatment or in the control group No signifi int changes were seen in free T4, free T3 or rT3 incentrations on any treatment, although free T3 as observed to decrease slightly during propranolol eatment Thus, the improvement of the clinical mptoms of hyperthyroidism cannot be explained by minished thyroid hormone concentrations in se im, since the reduction was small during propran ol and absent during atenolol treatment

y words thyroid hormones treatment β adrenergic ocking agents hyperthyroidism

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everal studies have indicated that β adrenoceptor locking drugs relieve many of the symptoms of yperthyroidism (12 19 21 23 26) The secretion f thyroxine (T4) from the thyroid (28) and the idioiodine uptake in the thyroid were unchanged 10) In recent studies a decrease in serum 3 3 5 iiodothyronine (T3) concentration was observed uring propranolol treatment (11 15 31) Further iore an increase in the serum concentration of 3 5 triiodothyronine (reverse T3 rT3) simulta eously with the decrease in the serum T3 concen ation was reported in patients with hyperthyroid m during short term treatment with propranolol ?7) Accordingly it has been proposed that β locking drugs influence the metabolism of T4 generating more biologically inactive rT3 than actr T3 (27)

In earlier studies on selective β 1 adrenoceptor blocking drugs practolol was used in the treatment of hyperthyroidism (18 19 26) This drug possesses some intrinsic sympathicomimetic activity which was suggested as an explanation of why practolol was inferior to propranolol in the treatment of hyperthyroidism (18 26) In the present study we evaluated the effects of atenolol a selective β 1 adrenoceptor blocking agent without intrinsic sympathicomimetic activity and compared them with the effects of propranolol on the symptoms and signs of hyperthyroidism Furthermore we investigated the effect of the drugs on the concentrations of total and free thyroid hormones in serum

PATIENTS AND METHODS

Twenty patients 16 females and 4 males aged 18–64 years (mean 45) with clinically moderate hyperthyroidism participated in the study None of them had been previously treated for thyroid disease Fourteen patients had a toxic diffuse goiter and six a toxic nodular goiter Patients initially evaluated after admission to hospital for seven days during which all clinical and biochemical investigations were performed

All patients were examined by one of the authors (O N) and evaluated clinically according to a clinical diagnostic index (CDI) (6) Basal metabolic rate (BMR) and electrocardiogram (ECG) were recorded in the morning under standardized conditions Oxygen consumption over a 10-minute period was determined twice during each investigation A thyrotropin releasing hormone (TRH) stimulation test (200 μg TRH i v) was performed in each patient

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Abbreviations T4=thyroxine T3=3 3 5-triiodothyronine rT3=reverse T3 (3 3 5 triiodothyronine) CDI=clinical diagnostic index BMR=basal metabolic rate TRH=thyrotrophin releasing hormone TSH=thyrotrophin ECG=electrocardiogram

Table I *Effects of propranolol or atenolol treatment on CDI and heart rate*

	Before treatment	After treatment	
		3 d	1 mo
CDI			
Propranolol (n = 10)	22±1	–	11±2***
Atenolol (n=10)	25±2	–	14±2***
Controls (n=8)	20±2	–	21±3[a]
Heart rate (beats/min)			
Propranolol (n=10)	92±3	72±3***	73±4***
Atenolol (n=10)	96±4	71±3***	75±5***
Controls (n=8)	92±4	–	91±4[a]

[a] Reexamined after 1–4 weeks
*** $p<0.001$ compared to pretreatment

(13) Blood samples were also drawn for radioimmunoassays of serum thyrotrophin (TSH) (20) T4 (17) T3 (17) rT3 (kit from Biodata) and free T4 and T3 after dialysis (7) Our normal ranges are TSH <7 mU/l T4 65–140 nmol/l T3 1 4–2 5 nmol/l rT3 0 14–0 54 nmol/l free T4 6 6–18 8 pmol/l and free T3 3 0–7 9 pmol/l Each hormone was assayed in duplicate and in the same series in each patient

After the initial investigations the patients were randomized into two groups for treatment Ten patients seven with diffuse and three with nodular goiters were treated with 40 mg of propranolol every 6 h The other ten with the same distribution of goiters received 50 mg atenolol every 6 h The doses chosen are considered to be potent in terms of the effect on isoprenaline induced cardia (2)

er three days of treatment a second BMR and ECG e recorded Thereafter patients were discharged for outpatient treatment for three weeks and then readmitted to the ward for two days whereupon all the initial investigations were repeated at the same time of the day

Eight untreated hyperthyroid patients (aged 44 years range 18–64) served as controls On two separate occasions they underwent an evaluation which included the CDI a TRH stimulation test and the analysis of thyroid hormones In seven hospitalized hyperthyroid patients without any treatment BMR was recorded on two sep arate days within one week to examine spontaneous v tions in the course of hyperthyroidism Only n changes were found

After the study 11 patients underwent subtotal roidectomy and three were treated with radioio Long term treatment with carbimazole and thyrox given to three patients and three continued on long treatment with β blocking agents

Statistical analysis was performed by Student s p t test Values are given as mean ± standard error mean (S E M)

RESULTS

Treatment with either propranolol or atenol sulted in a similar improvement of the clinical s toms and signs as indicated by the CDI an decrease in heart rate (Table I) The toleranc both agents was good and therapy was not drawn from any of the patients

Treatment for three days reduced BMR in the propranolol and the atenolol group by ($p<0.01$) (Table II) The BMR was examined third time after one month of treatment in 16 patients (9 propranolol and 7 atenolol treate these patients there was no significant diffe between the BMR obtained after three days of ment (250±11 ml/min) and after one month of ment (250±13 ml/min)

The serum TSH concentrations were low a not increase after TRH stimulation either bef during treatment The thyroid hormone conc tions in serum (total T4 T3 and rT3 and free T T3) before and during treatment are shown in III The serum T4 concentration did not cha any group Treatment with propranolol decr the T3 concentration from 4 6 to 3 9 ($p<0.05$) In the atenolol group there was no c in the T3 concentration Free T4 free T3 ar

Table II *Effects of propranolol or atenolol treatment on BMR (ml/min)*

Normal values are calculated with consideration to age sex height and weight according to standard tables

	Calculated normal value	Before treatment	After treatment	
			3 d	1 mo
Propranolol (n=10)	189±7	273±12	244±8**	239±8**[a]
Atenolol (n=10)	202±7	293±20	261±16**	266±26**[b]
Controls (n=7)	182±5	243±15	239±12	–

* $p<0.05$ ** $p<0.01$ compared to pretreatment values
[a] n=9 [b] n=7

able III *Ser ı c ncentr t ons of tl ıro d l or ones before and after o e montl s treatn ent th opr olol (n 10) or ‹ ten lol (10) and ı ntre ted l pertl ro l controls (ı 8)*

	Propranolol		Atenolol		Untreated hyperthyro d controls	
	Before treatment	Af er 1 mo treatment	Before treatment	Af er 1 mo treatment	F st v s t	Af er 1–4 weeks
4 (nmol l)	213+11	219+17	215+1?	201+17	230+14	218+18
3 (nmol l)	4 6+0 3	3 9+0 5*	5 0+0 4	4 8+0 5	4 6+0 7	4 3+0 4
T3 (nmol/l)	1 01+0 10	1 15+0 15	1 11+0 09	1 10+0 1?	1 17+0 13	1 14+0 12
ree T4 (pmol/l)	55+6	5?+9	51+4	53+6	55+7	55+8
ree T3 (pmol/l)	30+3	26+4	31+3	29+5	32+6	27±5

$p<0$ 05 compared to p e reatment

oncentrat ons d d not change during treatment th either of the β block ng drugs

DISCUSSION

Treatment w th the β block ng agents in pat ents vith hyperthyro d sm caused a similar reduct on in he hyperthyroid index and heart rate demonstrat ng favourable cl nical effects of both agents The ffect on heart rate was prompt and could be no iced after the first dose Treatment for one month l d not further lower the heart rate compared to the eg strat on on the third day

It has been shown earl er that non selective β lock ng agents are effect ve in reduc ng tremor in ,yperthyro d sm (9 16 18 19 23) but f ndings with he select ve β 1 block ng agent practolol have been ss certain (18) We found that the tremor d sap- eared in three pat ents treated with atenolol and in our treated w th propranolol In our op n on ate iolol was as effective aga nst tremor as propranolol

The beneficial effect of propranolol in the treat nent of hyperthyro d sm is well documented (21 3 26) However no study has been publ shed where the select e β 1 adrenoceptor blocking gent atenolol has been used w th equal efficacy Many of the cl n cal symptoms and s gns of hyper hyro d sm resemble those seen during β adrenerg c t mulat on n normal man Atenolol lacks intrins c ympath com met c act vity and this is probably an advantage in the treatment of hyperthyro d sm ompared w th other β block ng agents

The ncreased oxygen consumpt on n hyperthy ro d sm has been shown to be unchanged during treatment w th β block ng agents (8 12 32) or to decrease (22) During treatment w th both α and β blocking agents a sl ght decrease n oxygen con sumpt on has been found (24) Zwill ch et al (32) proposed that the metabol c abnormal t es seen in hyperthyro d sm are not med ated β adrenerg cally s nce they found no alterat ons during propranolol treatment but a normalizat on was seen when eu thyro d sm was ach eved after treatment w th rad o active iod ne Recently Saunders et al (2?) report ed a decrease in oxygen consumpt on in hyperthy ro d pat ents during propranolol treatment in the same dose as we have used They also observed a decrease in the serum T3 concentrat on by about 16% and proposed that the decrease in oxygen con sumption m ght poss bly be expla ned by reduced thyroid hormone concentrat ons at tissue level We found a sign ficant reduction of oxygen consump t on during treatment for three days w th proprano- lol as well as w th atenolol Th s reduct on pers sted during one month of treatment The discrepancy between unchanged total and free T3 concentra t ons in serum and the decrease in oxygen con sumpt on dur ng atenolol treatment do not support the suggest on that the fall in oxygen consumpt on is caused by a d m n shed serum T3 concentrat on Another reason for the decrease in oxygen con sumpt on dur ng β blockade may be the reduct on of the heart rate wh ch was sim lar in both treat ment groups

We found a small decrease in serum T3 concen trat on during propranolol treatment but no change was seen in the atenolol group There was a tenden cy for the free T3 concentrat on to decrease during propranolol treatment but th s change was not s gn f cant ($p<0$ 1) Earl er stud es have shown a fall n serum T3 concentrations during treatment with 80–160 mg propranolol da ly (11 25 31) Us ng

higher doses of propranolol (320 mg daily) Verhoeven et al (27) obtained a decrease in serum T3 in their patients although T3 still remained above the normal reference interval We used a moderate dose of each drug, which gave clinical improvement but caused no reduction of T3 concentration during atenolol treatment and only a small reduction during propranolol treatment Variations in the course of hyperthyroidism in different patients may explain divergent results during treatment with β-blocking agents In our hyperthyroid controls we registered small spontaneous variations in serum T3 concentrations

In a comparative study on the effects of propranolol and practolol in the management of hyperthyroidism Murchinson et al (18) noticed a decrease in serum T3 during propranolol but no changes during practolol treatment We used another selective β-1 adrenoceptor blocking agent, atenolol which did not influence the T3 concentration during treatment. It may be that the effects of propranolol on the metabolism of thyroid hormones involve β-2 adrenergic mechanisms

The peripheral conversion of T4 to T3 is decreased in various non-thyroidal diseases (3 4 30) and during treatment with dexamethasone (5 29) and propylthiouracil (1 14) Compared to other conditions acting on the conversion of T4 to T3 and T3 respectively the influence on the conversion drugs in hyperthyroid to be less in degree and importance The effect of these drugs seems to be mediated by a blockade at the cellular receptor level rather than an influence on the metabolism of thyroid hormones

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Angiotensin-Converting Enzyme in Sarcoidosis

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ABSTRACT Using a spectrophotometric assay with hippuryl L histidyl L leucine as substrate s angiotensin-converting enzyme (SACE) was determined in 85 sarcoidosis patients 116 healthy controls and 150 patients with various non sarcoid diseases The controls showed no sex or age variation and had SACE levels of 24 4±6 2 U/ml (mean ± 1 S D), giving a normal range (mean ± 2 S D) of 12 0–36 8 U/ml In contrast the sarcoidosis patients had SACE values of 38 4±14 4 U/ml with the highest values in cases with active sarcoidosis and duration of disease longer than two years (49 0±12 7 U/ml) A total of 41% of the sarcoidosis patients had elevated SACE, in the chronic active group 85% Patients with renal failure Hodgkin s disease and other malignant lymphoma had low SACE where as patients with lung cancer and tuberculosis had normal SACE values Among 266 patients with non sarcoid diseases and healthy controls only two had slightly elevated SACE but so far we have not found SACE above 40 U/ml in other than sarcoidosis patients An elevated SACE is rather specific in sarcoidosis and seems to be a useful supplement to existing diagnostic measures

Key words angiotensin-converting enzyme sarcoidosis Hodgkin s disease lung cancer renal failure

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The diagnosis of sarcoidosis is based on clinical signs chest X ray (CXR) and occurrence of non caseating epithelioid granulomas in tissue biopsy or Kveim Siltzbach test (13) For clinical purposes however the clinical picture together with a characteristic CXR is often sufficient (23) A Kveim Siltzbach test is positive in 50–90% of the cases (7) but as a high quality antigen is not generally available other ways have been proposed to confirm the diagnosis In this respect s lysozyme attracted attention some years ago because it was found to be elevated in many cases of active sarcoidosis (16) But as elevated values also occur in several other disorders s lysozyme is rather unspecific as a diagnostic test (15) Therefore Lieberman s first paper on elevated serum angiotensin-converting enzyme (SACE) in sarcoidosis (8) aroused great interest especially as only Gaucher s disease (11) and leprosy (12) have subsequently been associated with consistently elevated SACE

The purpose of the present study is to evaluate the diagnostic value of SACE analysis in a larger group of sarcoidosis patients compared with patients with other pulmonary diseases and diseases in which symptoms and signs might be caused by sarcoidosis

SUBJECTS

The series consisted of 85 sarcoidosis patients male female ratio 46 39 mean age 37 years (range 18–70) with a mean observation time of five years (range six months–37 years) All patients were of the Caucasian race

According to CXR at the time of blood sample the sarcoidosis patients were staged 0–III (18) Nineteen patients had no CXR abnormalities (stage 0) 22 had mediastinal lymphadenopathy alone (stage I) 35 had mediastinal lymphadenopathy and pulmonary infiltrations (stage II) and nine patients had pulmonary changes alone (stage III)

Because CXR staging corresponds only roughly to disease activity the patients were grouped as follows

(*a*) *Active sarcoidosis* Clinical signs of active disease including progressive or regressive changes in the CXR within the last two years These patients could be subdivided into (*aa*) *subacute* sarcoidosis with a duration shorter than two years and (*ab*) *chronic active* sarcoidosis with a duration of disease longer than two years

(*b*) *Inactive sarcoidosis* No signs of disease activity (or no changes in CXR) within the last two years mainly patients in a fibrotic stage of the disease

(*c*) *Remitted sarcoidosis* Resolved cases with no signs or residue of the disease at all clear CXR

Furthermore 150 sera were tested from patients with a variety of other diseases The controls were 116 healthy volunteers and blood donors aged 18–65 years

METHOD

The principle of a substrate analogue was used From the substrate Hippuryl-histidyl-leucine (HHL) ACE liberates

Abbreviations ACE=angiotensin-converting enzyme SACE=serum ACE CXR=chest X ray HHL=hippuryl-histidyl-leucine

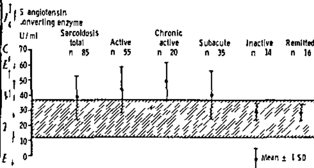


Fig 1 Distribution of SACE in 85 sarcoidosis patients subdivided into active inactive and remitted cases Hatched area=normal range

hippuric acid which can be measured spectrophotometrically (3) The modification of Lieberman (10) was used with some minor changes The calculations were made according to Lieberman (10) after correcting an error of calculation in his paper which yielded results three times too low (9) Blood samples were obtained by venipuncture and serum was stored at −20 C until analysis

The results are expressed as U/ml ACE units being equivalent to nmoles hippuric acid formed per minute at 37°C under standard assay conditions (10) A one hour assay was used SACE values are expressed in this paper as mean ±1 S D

The HHL was obtained during the first months from Calbiochem Luzerne Switzerland but later we used HHL from Bio-Science Products Reussbuhl Switzerland All sera tested with both substrates gave identical S CE values

statistical calculations were performed by Stu t test or χ^2 test Significance level was 5%

RESULTS

Control series

Among 116 healthy controls SACE was 24 4±6 2 U/ml (range 8 3–38 9) No sex or age differences

Table I *SACE (mean ± 1 S D) in 116 healthy controls and 85 sarcoidosis patients*

	N	SACE (U/ml)	*p*
Controls	116	24 4± 6 2	
Sarcoidosis total	85	38 3±14 4	<0 001
a) Active	55	43 4±15 3	<0 001
aa) Subacute	35	40 1±15 9	<0 001
ab) Chronic	20	49 0±12 7	<0 001
b) Inactive	14	29 1± 5 6	<0 01
c) Remitted	16	28 6± 5 5	
aa+*b*) Chronic cases	34	40 8±14 3	<0 001

Difference between *aa* and *ab* $p<0\ 025$
Difference between *a* and *b*+*c* $p<0\ 001$

were noted and food time of day or pro venous stasis had no influence on SACF Tl mal range of SACE was calculated as ±2 S D i e 12 0–36 8 U/ml

Sarcoidosis patients

Among 85 sarcoidosis patients SACE 38 4±14 4 U/ml which was significantly h than among the controls ($p<0\ 001$) SACE ir clinical subgroups of sarcoidosis is shown in F and Table I

The subgroup chronic active sarcoidosis ha highest mean values, significantly higher than subacute cases Inactive sarcoidosis and res cases had values within the normal range, but these groups had combined mean values higher the controls

Furthermore the proportion of patients wit vated SACE differed between the subgroups c coidosis (Table II) There was a trend tow higher percentage of elevated SACE among patients compared with female (22/46 (48% 13/39 (33%) respectively) but this differenc not significant and there were no differenc mean SACE between the sexes

No difference was noted between differen groups or between patients with or without pulmonary sarcoidosis Regarding the CXR s patients in stages 0 and III had lower values patients in stages I and II (mean 30 7 and 41 9 respectively) ($p<0\ 005$)

Other diseases

In addition 150 sera from patients with a vari diseases were analyzed (Table III) SACE i tients with lung cancer and tuberculosis was v the lower normal range but not significantly l than in the controls Malignant lymphomas sh

Table II *Incidence of elevated SACF in 85 coidosis patients*

	N	Patients with S >36 8 U/ml *n*	
Sarcoidosis total	85	35	4
a) Active	55	34	6
aa) Subacute	35	17	4
ab) Chronic	20	17	8
b+*c*) Inactive and remitted	30	1	

Table III *SACE (mean ±1 S D) and cases with elevated SACE among healthy controls and patients w[ith] diseases other than sarcoidosis*

	N	SACE (U/ml)	*p*	SACE >36 8 U/ml *n*	%
Controls	116	24 4+6 2		1	0 8
Lung cancer	26	22 8±5 5	n s		
Lung tuberculosis	7	22 6±5 9	n s		
Hodgkin s disease	23	21 3+7 6	<0 02	1	4
Other malignant lymphomata	18	20 4±6 8	<0 02		
Non sarcoid uveitis	20	24 1±7 0	n s		
Renal failure	15	20 3+6 9	<0 02		
Other diseases	41	25 2±6 7	n s		
Total	266			2	0 8

n s not significant

significantly low SACE But one patient with Hodgkin s disease had slightly elevated SACE 38 9 U/ml Furthermore 15 patients with non sarcoid renal failure had low SACE Normal SACE was found in four patients with non sarcoid hypercalcaemia due to cancer or primary hyperparathyroidism In contrast three patients with sarcoidosis hypercalcaemia and renal failure all had elevated SACE Normal SACE was also found in 37 patients with other diseases i e pneumonia various heart diseases arterial hypertension etc

In the total series only two non sarcoid patients out of 266 (one of the normal controls and one patient with Hodgkin s disease) had elevated SACE lower than 40 U/ml in both So far SACE higher than 40 U/ml has been found in this series only in sarcoidosis patients

DISCUSSION

ACE has an important place in the renin–angiotensin system by converting angiotensin I to angiotensin II It is located in the vascular endothelium probably in most organs but with far the highest concentrations in the lungs (22) Here it is found in small caveolae in the lung capillaries in close contact with the bloodstream (17)

Indeed it was surprising that Lieberman (8) reported high SACE in sarcoidosis because sarcoidosis had not been associated before with the renin–angiotensin system This finding has been confirmed in other studies using the same or different techniques (1 4 5 6 14)

Whether a high SACE reflects a high production in sarcoid tissue or a hampered decomposition is unknown But the finding of a ten fold higher ACE concentration in sarcoid lymph nodes (20)—together with signs of secretory function of the sarcoid epithelioid cells (2)—suggests that ACE is synthesized in sarcoid lymph nodes In contrast no increased ACE activity has been found in tuberculoid granulomas (20) or in experimental Freund s granulomas (21)

There has been disagreement concerning age and sex variations for SACE in normals (1 10) but in this series no differences were detected between males and females or between different age groups

This series confirms that SACE is elevated in sarcoidosis also in a Scandinavian population namely in 41% of the total series However there was a distinct difference associated with disease activity While inactive or resolved cases had nearly normal values 62% of the patients with active sarcoidosis had high SACE levels especially in the group with a chronic course longer than two years in which 85% of the patients had elevated SACE Only one of the normal controls and one patient with Hodgkin s disease had high SACE indicating a high specificity of SACE especially if an arbitrary upper limit of 40 U/ml is chosen So far we have found no patients without sarcoidosis with SACE higher than that

In other diseases which can give diagnostic difficulties with sarcoidosis (lung cancer tuberculosis uveitis lymphomata hypercalcaemia and renal failure) normal or low SACE values were found as in patients with a variety of other diseases Significantly low values in lung cancer have been reported

1 10 19) Although our patients with lung cancer had a rather low SACE their mean value did not differ significantly from that of the control group

The mean value of SACE in patients with Hodgkin s disease and other lymphomas was significantly lower than in controls However as mentioned above one patient with Hodgkin s disease had an elevated SACE (but lower than ~0 U/ml)

It was of special interest to note that patients with renal failure and/or non-sarcoid hypercalcaemia had low or normal SACE since s-lysozyme is elevated both in active sarcoidosis and in renal failure (15) and therefore is of no diagnostic value in evaluating hypercalcaemic states with renal failure which occasionally may be caused by sarcoidosis But it is necessary to draw the blood sample before initiation of prednisone treatment because corticosteroids seem to normalize a high SACE in sarcoidosis (19)

It seems that SACE should be a useful diagnostic tool for the clinician though without replacing a careful clinical examination CXR and in many cases histological evidence of non-caseating epithelioid granulomas A high SACE nearly always indicates active sarcoidosis while a normal SACE is of doubtful value in this respect Furthermore SACE probably may be valuable in following the course and effect of treatment (19) but in this respect one must wait for the results from long term studies

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The Expression of a Human B-Lymphocyte Antigen on Cells in Different Types of Leukaemia

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BSTRACT The expression of a B-cell antigen on e surface of leukaemic cells from patients with var- us forms of leukaemia was studied by direct im unofluorescence using a rabbit antiserum against ronic lymphocytic leukaemia (CLL) cells The an- gen was found on normal peripheral blood B-lym hocytes and on the majority of lymphocytes from itients with CLL Most normal peripheral blood onocytes and blasts from patients with acute my oblastic leukaemia acute myelomonocytic leu aemia or acute lymphoblastic leukaemia of T-cell pe did not carry the antigen but a minority of such lls were weakly stained In two of three patients th blast transformation of chronic myelocytic leu emia, a high proportion of the blasts carried the itigen It was also found on the surface of the hairy ells from two cases of leukaemic reticuloendothelio-

These cells also carried Fc receptors and immu globulin with restricted heterogeneity (mu, lambda d alpha mu delta kappa, respectively) The cellu distribution of the B-cell antigen differs to some tent from that of Ia like antigens detected by anti ra against purified B-cell membrane products The monstration of the antigen as well as immuno- lobulin of a single light chain type on the surface of iry cells strongly supports the B-lymphocyte origin these cells

y words B-cell antigen surface membrane immuno- obulin leukaemia leukaemic reticuloendotheliosis

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lymphocytes can be identified by heterologous ntisera raised against whole B-cells or B-cell mem rane products Such antisera may vary in their actions with different cells Most antisera raised ainst enzyme or detergent solubilized cell mem ane preparations seem to detect antigens which e related to the Ia antigens in rodents (5 15 22 33 34 37) These antisera block the reaction of uman alloantisera with B lymphocytes as well as the stimulation in mixed lymphocyte culture and the chemical structure of the antigen is similar to that of mouse Ia antigens (6 25 33 37) In man Ia-like antigens have been detected not only on B lymphocytes (normal peripheral blood B-lym phocytes chronic lymphocytic leukaemia (CLL) lymphocytes lymphoblastoid B-cell lines) but also on monocytes blasts in acute lymphocytic leukae mia of non T non B cell type blast crisis in chron ic myelocytic leukaemia (CML) and most cases of acute myeloblastic leukaemia (AML) (5 32 33 34 37 39) They are also present on immature blast cells in normal bone marrow but not on more dif ferentiated cells in the myeloid series (23 36)

We have recently reported on a heterologous an tiserum against CLL lymphocytes that identifies a B-cell-specific antigen not identical with Ia antigens (4) This report concerns the distribution of this antigen on the cells in different forms of leukaemia

STUDY POPULATION

Healthy individuals This group consisted of 10 members of the laboratory staff Only peripheral blood mononu clear cells were examined

Chronic lymphocytic leukaemia All 11 patients had pe ripheral blood lymphocytosis and a diffuse lymphocytoid infiltration of the bone marrow Only peripheral blood was examined

Acute leukaemia Five of the 11 patients in this group had AML two acute myelomonocytic leukaemia

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Abbreviations CLL=chronic lymphocytic leukaemia CML=chronic myelocytic leukaemia AML=acute my eloblastic leukaemia AMML=acute myelomonocytic leukaemia ALL=acute lymphoblastic leukaemia FITC=fluorescein-isothiocyanate TRITC=tetramethyl rhodamine-isothiocyanate PBS=phosphate-buffered sa line BSA=bovine serum albumin SRBC=sheep red blood cells sIg=surface membrane immunoglobulin

(AMML) one acute lymphoblastic leukaemia (ALL) and three blastic transformation of CML All patients had a high peripheral WBC with a dominance of blasts Further classification was based on cell morphology intracellular peroxidase staining and serum and urine lysozyme deter minations

Hairy cell leukaemia Both of the two patients had cir culating mononuclear cells with a typical hairy appearance in phase contrast microscopy and with high activity of tartrate resistant acid phosphatases Both patients were treated by splenectomy and the diagnosis of leukaemic reticuloendotheliosis was confirmed on histological ex amination of the large spleens Agarose gel electrophore sis of plasma and urine revealed no monoclonal Ig in either case

METHODS

Antisera An anti B-cell serum (antiserum 7420) was raised in one rabbit by immunization with lymphocytes from a patient with CLL The preparation of FITC (fluorescein isothiocyanate) labelled F(ab)₂ fragments of antiserum IgG absorptions and testing for B lymphocyte specificity have been described earlier (4) FITC labelled F(ab)₂ fragments of IgG from normal rabbit serum were prepared according to the same procedure

FITC-labelled antisera against alpha mu gamma and delta heavy chains TRITC (tetramethyl rhodamine iso thiocyanate) labelled polyvalent antiserum against human Ig heavy and light chains and TRITC labelled F(ab)₂ fragments of goat antihuman Fab were obtained from Nordic Immunological Laboratories Tilburg the Nether lands FITC labelled antisera against kappa and lambda chains were from Dakopatts Copenhagen Denmark labelled F(ab)₂ fragments of rabbit IgG against mu and lambda chains were produced at the laboratory ing the method of Forsum (14) The specificity of conjugates was tested on myeloma and macroglobulin aemia bone marrow smears as described earlier (35) To stain all cells with surface membrane Ig the TRITC labelled polyvalent whole IgG was used in the early phase of the study and the TRITC labelled F(ab)₂ fragments were used later Since no difference in sIg positive cells in healthy individuals was observed these groups are not reported separately

Latex phagocytosis The mononuclear cells from periph eral blood were suspended in medium RPMI 1640 at a concentration of 1×10^6 cells/ml 0 020 ml of 0 8 mu latex particles (Bacto) were added to 10 ml of the cell suspen sion After incubation for 60 min at 37 C in a water bath the cells were washed with prewarmed PBS-BSA (phos phate buffered saline pH 7 2 with 1% bovine serum albumin) twice before immunofluorescent staining

Immunofluorescence One drop (approximately 30 μl) of the cell suspension containing $1\ 5\times10^6$ cells was mixed with one drop of the FITC or TRITC conjugate in plastic tubes These were incubated at +4 C for 30 min with intermittent shaking The cells were washed twice with PBS-BSA at +4 C and mounted in buffered glycerol pH 7 8 The slides were examined in a Leitz Orthoplane flu orescence microscope equipped with epi illumination and filter systems for narrow band excitation of FITC TRITC (20) The cells were first identified in phase trast transmitted light and then examined fluorescence with incident light Two hundred cells the typical morphology of small lymphocytes ined and the percentage of fluorescent cells was culated In the CLL patients larger lymphoid cells sometimes more abundant and were included In the preparations from patients with acute leukaemia leu mic reticuloendotheliosis and hairy cells respectively blasts were identified by their morphology in trast and the percentage of these cells with memb fluorescence was calculated In the cell preparations for staining of monocytes these were identified by phology or by intracellular accumulation of latex part To demonstrate intracellular peroxidase the cells smeared on glasses after the immunofluorescence stai fixed with formalin and stained by the method of Ka (24) No counterstain was applied but the slides mounted in buffered glycerol and the percentage of p idase positive cells with membrane fluorescence were culated

Detection of receptor for Fc of IgG and for sheep e rocytes (E rosettes) Rhodamine conjugated heat a gated human IgG was prepared as described previ (4) It was used for immunofluorescence staining of n nuclear cells as described above E rosettes were pared according to Pattengale and Reichelderfer (27) Ficoll to stabilize the rosettes

RESULTS

Peripheral blood mononuclear cells in healthy individuals

The percentage of small lymphocytes stained the 7420 conjugate (mean 12 5% range 9–22) in close agreement with the percentage of su membrane immunoglobulin (sIg) positive lymphocytes (mean 12 7% range 9–23 5 Tab In seven individuals when staining for sIg an cell antigen was performed simultaneously the centage of B cells obtained by the two methods very similar (Fig 1)

Peripheral blood monocytes were examine one healthy individual using three different meth to identify the cells morphology in phase cont microscopy phagocytosis of latex particles staining for intracellular peroxidase The perce age of monocytes in mononuclear cell suspensi was very similar by these three criteria 27 33 33% respectively The staining reaction with 7420 conjugate however varied somewhat weak positive reaction was obtained with a s population of monocytes identified by morpholo in phase contrast microscopy or latex phagocyto

Table I *Peripheral blood lymphocytes in healthy individuals and patients with CLL % of cells with 7?0 B-cell antigen and with sIg (stained with FITC labelled F(ab')₂ fragments of antihuman Fab or TRITC-labelled IgG against human Ig)*

	Lymphocytes (%)	
	B-cell antigen-positive	sIg-positive
Healthy individuals		
Mean	1?.5	1? 7
Range	9–22	9–23.5
n	10	10
CLL patients		
Mean	69	84
Range	22 100	76–99
n	1?	7

Table II *Peripheral blood blast cells in patients with AML AMML ALL or blast transformation (BT) of CML (% of cells stained with 7470 antiserum)*

Case no	Diagnosis	Positive cells (%)
1	AML	<0.5
2	AML	<0.5
3	AML	6.5
4	AML	5.5
5	AML	1 0
6	AMML	? 5
7	AMML	4 0
8	BT of CML	34 0
9	BT of CML	47 0
10	BT of CML	3 0
11	ALL	? 0

?1 and 13% respectively) while in the majority of the monocytes there was no certain staining The peroxidase-positive cells were all unstained with the FITC conjugate In all preparations a subpopulation of small lymphocytes (9–12%) stained with a strong and distinct membrane fluorescence

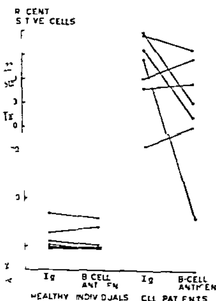


Fig 1 Peripheral blood lymphocytes in healthy individuals and patients with CLL Percentage of cells with 7470-B-cell antigen and with sIg (stained with TRITC-labelled F(ab')₂ fragments of antihuman Fab or TRITC labelled IgG against human Ig)

Chronic lymphocytic leukaemia

In CLL the majority of peripheral blood lymphocytes carried the B-cell antigen (Table I) Staining for sIg was performed in 7 cases A difference was sometimes observed between the number of sIg and B-cell antigen positive cells (Fig 1) Staining with anti kappa and anti lambda antisera disclosed a monoclonal proliferation in all 7 cases

Acute leukaemia

The majority of blasts from the peripheral blood of patients with acute leukaemia or AMML were negative (Table II) In many cases however a minority of the blasts were clearly positive (1 7%) and a portion of the others stained very faintly (classified as negative) In 2 of 3 cases of blast transformation of CML a large proportion of the blasts were positive In one case of acute lymphocytic leukaemia only 5% of the blasts were positive while 89% carried T-cell marker In all other cases of acute leukaemia the cells lacked sIg or receptor for sheep erythrocytes The cells from the patients with AMML carried Fc receptors detected by rhodamine-conjugated aggregated human IgG

Hairy cell leukaemia

In both patients a large proportion of the hairy cells carried Fc receptors as demonstrated by their ability to bind aggregated human IgG (Table III) The number of cells with receptor for sheep red blood cells (SRBC) was low and in general these cells had

Table III *Surface markers and phagocytic capacity of circulating hairy cells in leukaemic reticuloendotheliosis*

Case no	Mononuclear cells ×10⁹/l	Mononuclear cells Hairy cells (%)	Hairy cells (%) with receptor for SRBC (E rosettes)	Hairy cells (%) with receptor for Fc (aggregated IgG)	Phagocytizing hairy cells
1	4 6	74	<1	91	n t
2	1 5	32	27*	81	76

Per cent of all mononuclear cells
n t = Not tested

the appearance of small lymphocytes though morphological classification of the rosetting cell was sometimes difficult In the only case examined 76% of the hairy cells phagocytized latex particles but the number of ingested particles was smaller *than in mature monocytes and the possibility that* they had been adsorbed to the cells could not be entirely excluded In both cases the majority of the hairy cells carried 7420-B-cell antigen as well as sIg (Table IV) In case 1 only mu and lambda chains were detected while immunoglobulin chains of the four major classes were found in case 2 even if the staining with anti alpha and anti lambda was weak and the number of IgG positive cells was low When the staining was performed with F(ab) fragments anti kappa and anti lambda antisera only kappa [illegible]ins were detected

DISCUSSION

The antigen(s) identified by 7420 antiserum was detected on normal peripheral blood B lymphocytes and on lymphocytes from patients with CLL a monoclonal proliferation of B lymphocytes (1 28) It was also present on the blasts from 2 of 3 cases of blast transformation of CML This distributio[illegible] similar to that of Ia like antigens On the contr[illegible] only a minority of normal peripheral blood m[illegible] cytes and blasts from patients with acute m[illegible] cytic leukaemia or AMML were positive and [illegible] *staining was weak No case of ALL of non T* [illegible] B type was examined This distribution profile [illegible] fers from that reported for Ia like antigens Si[illegible] results have been reported by others using ra[illegible] antisera against whole CLL lymphoblastoid [illegible] line or monkey B-cells A negative reaction [illegible] monocytes was obtained in 2 of 3 reports (2 8 [illegible] and negative reactions with AML cells in 3 of 3 [illegible] ports (9 10 21) The reason for these difference[illegible] not quite clear It is possible that antisera produ[illegible] against whole cells after the necessary absorpti[illegible] are so weak that small amounts of antigen canno[illegible] detected In fact studies using the fluoresce[illegible] activated cell sorter have demonstrated m[illegible] smaller amounts of Ia like antigen on AML c[illegible] and monocytes than on ALL cells cells from b[illegible] transformation of CML and B lymphocytes O[illegible] 20% of monocytes were weakly positive and so[illegible] AML cases were completely negative (23) I[illegible] however equally possible that antisera ra[illegible]

Table IV *Surface Ig and 7420-B cell antigen on circulating hairy cells in two cases of leukae[illegible] reticuloendotheliosis*

Case no	Hairy cells stained with FITC-labelled IgG against Ig chains (%) α	μ	γ	δ	κ	λ	Hairy cells stained with FITC-labelled F(ab)₂ fragments of IgG against Ig chains and 7420-B-cell antigen (%) μ	κ	λ	7420
1	<1	89	1	n t	<1	97	96	n t	97	94
2	88	76	10	89	95	84	n t	88	<1	92

* Faint staining
n t = Not tested

inst whole B lymphocytes may detect antigen ...er than Ia like antigens In fact this seems to be case with the 7420 antiserum since inhibition d capping experiments clearly indicate that the tigen detected is different from Ia like antigen ell antigen not identical with Ia like antigen was o reported by Balch et al (2 3) using an anti nkey B cell serum

The nature and origin of the hairy cells in ıkaemic reitucloendotheliosis are controversial ey have been considered to be of B lymphocyte igin belong to the monocyte–histiocyte series or be unique cells differing structurally as well as nctionally from B lymphocytes as well as mono tes The arguments in favour of these hypotheses ve recently been reviewed by Catovsky (12) and ve since then been the subject of several reports 11 13 16 17 18 26 29 30 31 38) In the two ses presented here the cell surface marker idies suggest a near relation of the hairy cells to lymphocytes The cells were clearly stained with e 7420 antiserum which gave only a weak staining a minority of normal monocytes and failed to act with the monocytoid cells from two cases of MML The sIg was clearly monoclonal in case 1 d when stained with F(ab) fragments only one ht chain type was detected in case 2 It seems that preincubation at 37 C was sufficient to remove ost of the IgG which was probably bound in vivo Fc receptors A receptor for the Fc part of IgM s recently been found on hairy cells (11) and it nnot be completely excluded that the IgM de ted was adsorbed to the cell surface This seems wever very unlikely since only one light chain pe was found and there was no evidence of a onoclonal Ig in plasma or urine The nature of the aining for IgD and the weak staining for IgA can ot be determined since F(ab) fragments of these itisera were not available

While the finding of Ig with restricted het ogeneity on hairy cells has been reported sev al times (7 12 13 17 18) we have not found any ports on the occurrence of B-cell antigen defined y anti-CLL antisera Four cases have been kamined with antisera against Ia like antigens hich have also been found on the cells (5 13 37)

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The Expression of a Human B-Lymphocyte Antigen and Surface Membrane Immunoglobulin by Lymphoid cells from Patients with Lymphocytic Lymphoma, Multiple Myeloma and Benign Monoclonal Gammapathy

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STRACT Lymphoid cells from patients with iphocytic lymphoma, multiple myeloma or benign noclonal gammapathy (BMG) were examined by ect immunofluorescence for the expression of sur e membrane immunoglobulin (sIg) and B-cell an n defined by a rabbit antiserum against chronic iphocytic leukaemia lymphocytes This antiserum been shown to detect a B cell antigen different m Ia like antigen In well differentiated lymphoic lymphoma, the cells carried the B-cell antigen well as one class of heavy and light Ig chain A culating monoclonal lymphocyte population was ularly found in the blood although the lymphocyte nber was not increased In multiple myeloma the nber of circulating cells carrying mu chains was all the depression being most pronounced in pa- its who had been treated with cytostatics A noclonal population of lymphocytes expressing the isotype(s) of the M component was found in the od in 6/15 cases and more often in patients with vanced disease The number of cells with B cell igen agreed fairly well with the number of Ig posi cells indicating that the B cell antigen was ex ssed on normal as well as myeloma related lym ocytes A dissociation *of the expression of the anti* is was however observed in two cases (one lymphoic lymphoma, one myeloma) with a large number cells with B-cell antigen but a small number of cells h sIg The B-cell antigen was usually not detected the surface membrane of Ig-containing plasma ls from patients without monoclonal gammapathy from the majority of patients with BMG but on a ying proportion of myeloma cells The tentative iclusion is drawn that the B-cell antigen is a dif entiation antigen which is gradually lost during B- nphocyte differentiation but is retained to some ex it on myeloma cells as an expression of a lower gree of maturity

Key words B-cell antigen surface membrane immunoglobulin myeloma benign monoclonal gammapathy lymphoma

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Chronic lymphocytic leukaemia (CLL) and most cases of lymphocytic lymphoma are B-cell proliferations where the majority of the cells are frozen at the maturation level of B lymphocytes (2 21) A minor part of the malignant clone may mature to immunoglobulin secreting cells and in such cases a monoclonal spike usually of IgM type is found in the plasma (21 27) Multiple myeloma and benign monoclonal gammapathy (BMG) are B-cell proliferations where the majority of the cells have matured to Ig secreting cells and an M-component in plasma and/or urine is found with few exceptions According to several reports the malignant clone is however also represented at the B lymphocyte level (1 7 13 18 21) B-cell antigens defined by heterologous antisera against whole B-cells or B cell membrane products (Ia like antigens) are readily demonstrated on the surface of lymphocytic lym

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Abbreviations CLL=chronic lymphocytic leukaemia BMG=benign monoclonal gammapathy WDL=well differentiated lymphocytic lymphoma DWDL diffuse WDL NWDL=nodular WDL DPDL=diffuse poorly differentiated lymphocytic lymphoma DHL=diffuse histiocytic lymphoma FITC fluorescein-isothiocyanate TRITC=tetramethyl rhodamine-isothiocyanate sIg=surface membrane immunoglobulin PBS=phosphate-buffered saline BSA=bovine serum albumin IFL immunofluorescence k/l ratio=the ratio of kappa positive to lambda-positive cells

phoma cells (14 16) whereas conflicting results are reported regarding the expression of B-lymphocyte antigens on the surface of plasma cells (3 6 11 24)

We have recently reported on a heterologous antiserum against CLL cells that identifies a B-cell specific antigen not identical with Ia like antigen (5 28) The present report concerns the distribution of this antigen on lymphocytic lymphoma cells as well as on normal and malignant plasma cells We also report on the occurrence of circulating monoclonal B-lymphocyte populations in the peripheral blood in patients with lymphocytic lymphoma and multiple myeloma.

STUDY POPULATION

Healthy individuals This group consisted of 10 members of the laboratory staff Only peripheral blood mononuclear cells were examined

Myeloma All 24 patients had an M-component in plasma and/or monoclonal light chains in the urine and subnormal levels of at least one Ig class They also fulfilled at least one of the following criteria. ≥10% plasma cells in a bone marrow smear or osteolytic lesions demonstrated by X-ray examination The M-component was of IgG type in 12 cases IgA in 6 IgD in 2 and only light chains in 4 cases Bone marrow and peripheral blood were examined in 6 patients blood only in 9 and bone marrow only in 9 Ten patients were examined before treatment and 14 had been on cytostatics Clinical stage was estimated according to [illegible]e and Salmon (8)

[illegible]ign monoclonal gammapathy All 8 BMC patients [illegible]d an M-component in plasma with or without small amounts of monoclonal light chains in the urine but no osteolytic lesions at X-ray examination There was no change or a very slow progress in M-component concentration (i e an increase of at most 2 g/l per year) during an observation time of at least two years (mean 59 months) The M-component was of he IgG type in 5 patients and of the IgA type in 3

Malignant lymphoma Seven of 9 patients had well differentiated lymphocytic lymphoma (WDL) In three of these it was diffuse (DWDL) in one nodular (NWDL) and in three cases no further classification was made One patient had diffuse poorly differentiated lymphocytic lymphoma (DPDL) and one diffuse histiocytic lymphoma (DHL) according to the classification of Rappaport Eight patients had bone marrow involvement Lymphoma tissue (bone marrow lymph node or spleen) was examined in 4 patients and peripheral blood in 8

METHODS

Antisera An anti-B-cell serum (7420) was raised in one rabbit by immunization with lymphocytes from a patient with CLL The preparation of FITC (fluorescein isothiocyanate)-labelled F(ab)₂ fragments of IgG antiserum absorptions and testing for B-lymp specificity have been described earlier (5) FITC F(ab) fragments of IgG from normal rabbit prepared according to the same procedure

FITC-labelled antisera against alpha mu gamm delta heavy chains TRITC (tetramethyl rhoda isothiocyanate)-labelled polyvalent antiserum a human Ig heavy and light chains and TRITC F(ab)₂ fragments of goat antihuman Fab were from Nordic Immunological Laboratories Tilbu Netherlands FITC-labelled antisera against kapp lambda light chains were from Dakopatts C Denmark The specificity of the conjugate was tes myeloma and macroglobulinaemia bone marrow sm described earlier (27) To stain all cells with surf brane Ig (sIg) the TRITC labelled polyvalent who was used in the early phase of the study and the labelled F(ab)₂ fragments were used later Since ference was observed in sIg positive cells in healh viduals they are not reported separately

Preparation of cells Mononuclear cells were from heparinized venous blood by the Ficoll-met method They were suspended in PBS (phospha fered saline pH 7 2) containing 1% BSA (bovine albumin) at a concentration of 4×10⁶/ml and ke water-bath at 37°C for 45 min After washing twi prewarmed PBS-BSA the cells were suspended BSA for immunofluorescent (IFL) staining

Bone marrow was aspirated from the sternum iliac crest and a single-cell suspension was described earlier (26) The cells were incubated at 45 min as described above Cytocentrifuge smea made from each cell suspension for intracellular s Single-cell suspensions from lymph nodes or splee obtained by fine needle aspiration or by grinding material through a Borel press

Immunofluorescence

Peripheral blood mononuclear cells One drop mately 30 μl) of the cell suspension containing cells was mixed with one drop of the FITC or conjugate in plastic tubes These were incubated for 30 min with intermittent shaking The cell washed twice with PBS BSA at +4 C and mou buffered glycerol pH 7.8 The slides were exami Leitz Orthoplane fluorescence microscope equipp epi-illumination and filter systems for narrow band tion of FITC and TRITC (12) The cells were fir tified in phase contrast with transmitted light a examined for membrane fluorescence with incide Two hundred cells with the typical morphology o lymphocytes were examined and the percent fluorescent cells was calculated In the lympho tients larger lymphoid cells were sometimes more dant and were included

Bone marrow cells One drop of the cell susp containing 150 000 cells was mixed with one drop conjugate (FITC-labelled F(ab)₂ fragments of 74 tiserum or of normal rabbit IgG) After incubati washing as described above cytocentrifuge slide prepared the cells were fixed in acetone at −20°C min and stained for intracellular Ig using a poly

Table I *Peripheral blood lymphocytes in patients with malignant lymphoma percentage of cells with sIg with 7420 B cell antigen*

Case	Diagnosis	Stage	M-component Type	M-component Concentration (g/l)	Lymphocytes (×10⁹/l)	Percentage of lymphocytes stained with antisera against κ	λ	7420 B cell antigen
	DHL	IA	GK	6	0 8	5 0	3 0	7 5
	DWDL	IVA	GK	24	3 8	<1 0	<1 0	33 0
	DWDL	IVA	MK	10	3 5	3 5	0 5	6 5
	WDL	IVB	MK	4	1 9	33 0	3 5	36 0
	DPDL	IVB	MK	8	5 7	79 0	0 5	44 0
	WDL	IVA	ML	11	1 1	0 5	4 5	5 0
	WDL	IVB	–		0 6	35 5	<0 5	30 0
	DWDL	IVA	–		3 0	45 0	2 0	40 5
	NWDL	IVA	–		11 0	19 0	1 0	28 0
Healthy individuals (N=7)			–		1 4–4 0	8 2	4 2	12 5

FITC labelled antiserum against human Ig heavy and light chains (26) The slides were washed and mounted in buffered glycerol They were examined first in TRITC fluorescence to identify cells with a homogeneous intracytoplasmic fluorescence and plasmacytoid morphology and then in FITC fluorescence to identify cells with fluorescence Two hundred Ig-containing cells were examined and the percentage of surface stained cells was calculated

Mitogen stimulation

Peripheral blood mononuclear cells from one healthy individual were cultured in medium RPMI 1640 together with Staphylococcus aureus strain Cowan I as described elsewhere (4) The cultures were provided by G Banck Department of Bacteriology Malmö General Hospital After 4–5 days culture the cells were spun down washed several times in PBS BSA and stained with FITC labelled F(ab)₂ fragments of 7420 antiserum as described above

RESULTS

Malignant lymphoma

In three patients with WDL and bone marrow involvement the majority of bone marrow lymphoid cells were stained with 7420 antiserum and by either anti kappa or anti lambda antiserum indicating a monoclonal proliferation The number of 7420 positive cells agreed fairly well with the number of sIg positive cells Similar results were obtained with cell suspensions from a lymph node and spleen from one patient each In the peripheral blood staining for sIg disclosed a monoclonal lymphocyte population i e the ratio of kappa positive to lambda positive cells (k/λ ratio) ≥4 0 or ≤0 5 (normal range 1 3–2 6) in 6 of 7 cases of WDL or PDL but not in the patient with DHL (Table I) The number of 7420-positive cells agreed in general well with the number of Ig positive cells (Fig 1) One patient with a very low number of sIg positive cells (1 %) had a high percentage of 7420-positive cells (33 %)

Multiple myeloma

In multiple myeloma the number of sIg positive peripheral blood lymphocytes varied widely the mean value being somewhat lower than in healthy

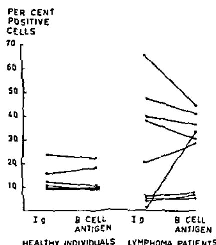


Fig 1 Peripheral blood lymphocytes in healthy individuals and patients with malignant lymphoma Percentage of cells with 7420-B-cell antigen and with surface membrane Ig (stained with TRITC labelled F(ab)₂ fragments of anti Fab or with TRITC labelled polyvalent IgG against human Ig)

Table II *Peripheral blood lymphocytes in healthy individuals and patients with multiple my percentage and absolute number of cells with 7420 B cell antigen and with sIg (stained with f fragments of anti Fab or with anti mu)*

		B-cell antigen positive lymphocytes		sIg positive lymphocytes stained with antiserum against			
				Fab[a]		mu	
		%	×10⁶/l	%	×10⁶/l	%	×1(
ealthy individuals	Mean	12 5	246	12 7	249	10 2	19
	Range	9–22	156–403	9–23 5	147–431	7 5–14 5	13
	N	10	7	10	7	7	7
ultiple myeloma intreated	Mean	10 2	209	9 7	190	7 0	149
	Range	5–15	95–298	4–13 5	67–269	4–11 5	75
	N	7	6	7	6	6	5
ultiple myeloma reated	Mean	8 1	208	5 8*	88*	2 4**	36
	Range	3 5–27	10–875	1–20	9–458	1–3 5	1
	N	8	8	8	8	7	7

$p<0.05$ ** $p<0.001$
Whole IgG against human Ig heavy and light chains was used in some early cases

idividuals (Table II) This difference was more ronounced in patients who had been treated with ytostatics They had a significant depression of the umber of sIg positive lymphocytes ($p<0.05$) In 6 f 15 cases (3 untreated 3 treated with cytostatics) iere was an imbalance in the k/l ratio with the jority of B lymphocytes carrying the same class light chain as that of the M component (Table) The number of sIg positive lymphocytes in creased substantially in only one of these six cases (Fig 2) An abnormal k/l ratio was seen more often in patients with myeloma of clinical stage III (5/7) than among those with clinical stage II (1/8) No pa tient with myeloma of clinical stage I was examined

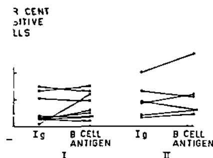
In 3 patients (nos 2 4 5) the majority of th phocytes also carried the same class of heav as that of the M component In 2 patients (no lymphocytes carrying mu chains were but several cells carried the heavy chain M-component and might well be responsible change in the k/l ratio As double staining w performed it cannot be determined wheth carrying mu chains were restricted to mainly or lambda chains

The number of B-cell antigen positive cel also somewhat smaller in myelo myeloma in particular The difference was l nounced than with sIg positive lymphocyt

Table III *Peripheral blood lymphocytes in patients with multiple myeloma and a monoclonal disti of sIg positive cells percentage of cells carrying Ig heavy and light chains and 7420 B cell antigen*
Cases 1–3 were examined before treatment

Case no	M-component heavy and light chain	Percentage of lymphocytes stained with antisera against						
		κ	λ	α	μ	γ	ε	7420
1	GK	10 0	1 0	n t	n t	n t	n t	11 0
2	AK	8 5	2 0	10 5	3 5	1 0	n t	12 0
3	AK	4 0	1 0	2 0	5 0	1 0	n t	6 0
4	GL	2 0	6 0	1 0	2 0	8 0	n t	6 0
5	DL	2 0	21 0	1 0	2 5	0 5	21 0	27 0
6	GK	5 5	1 0	0 5	3 0	1 5	n t	4 5
Healthy individuals (N=7)		8 2	4 2	2 3	10 2	0 7		12 5

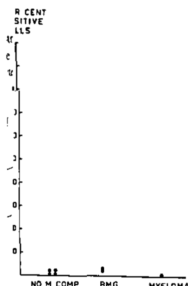
n t =Not tested



2 Peripheral blood lymphocytes in patients with mul le myeloma Percentage of cells with 7420 B-cell anti n and with sIg (stained with TRITC labelled F(ab)₂ gments of anti Fab or with TRITC labelled polyvalent G against human Ig) I=patients with a k/l ratio of 0 8– 3 II=patients with k/l ratio of <0 3 or ≥4 0

itistically insignificant In most cases there was ose agreement between the number of sIg positive lls but one exception was noted (Fig 2) In this se the number of B cell antigen positive cells (?%) exceeded considerably the number of sIg ositive cells (1%) This patient had multiple yeloma of stage III

Bone marrow plasma cells from patients without onoclonal gammapathy or lymphoproliferative sease did not carry the B-cell antigen (Fig 3) In ents with BMG the number of positive plasma lls was also mostly small with some exceptions



ig 3 Ig-containing bone marrow plasma cells in patients with multiple myeloma BMG or without an M-compo nent Percentage of cells with 7420-B-cell antigen

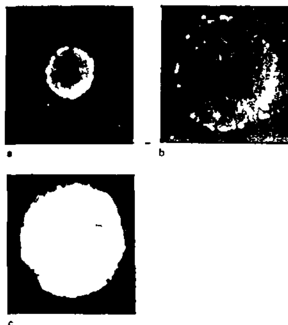


Fig 4 A small lymphocyte (a) and a plasma cell (b) stained in suspension with FITC labelled F(ab)₂ frag ments of 7420 antiserum and examined in FITC fluores cence The same plasma cell is also seen after fixation (c) staining for intracellular Ig with TRITC labelled anti Ig and examination in TRITC fluorescence Kodak Tri X Pan×1250

In contrast the antigen was expressed on the mem brane of a varying proportion of plasma cells from patients with multiple myeloma Although some myeloma cases were negative and considerable overlapping was observed the number of positive cells in myeloma patients differed significantly from that in patients with BMG ($p<0.01$) or without an M component ($p<0.005$) The fluorescence pattern of the myeloma cells was clearly different from that of B lymphocytes While these had a distinct homogeneous confluent membrane fluorescence the positive plasma cells were very weakly stained with a sparse granular fluorescence (Fig 4) In the two cases of BMG with a large number of B-cell antigen positive cells less than 2% of plasma cells containing light chains of another class than that of the M-component carried the B cell antigen Such studies were not performed on the plasma cells from myeloma patients

Mitogen stimulated peripheral blood lymphocytes

In 4 5 and 7 day cultures of peripheral blood mononuclear cells together with the mitogen

nber of bone marrow plasma cells containing Ig other classes than that of the M-component (27) eems that the depress on of other clones is at st part ally expressed already at the B lymphoe level On the other hand a circulat ng popula n of lymphocytes wh ch express the idiotype of M-component exists in most cases of myeloma me of them seem not to react read ly with anti itypic antisera but some probably do as in some eloma cases the lymphocytes express predomi ntly k or l chains Such monoclonal lymphocyte pulations may be more common in patients with vanced disease In this connection the results h 7470 ant serum m ght be of some interest In neral there was a good agreement between the mber of sIg pos tive lymphocytes and the B-cell igen positive cells in polyclonal as well as monoclonal cases ind cating that both the nor al and the myeloma related lymphocytes carry the tigen In one case the number of B-cell ant gen sit ve lymphocytes exceeded considerably the mber of sIg pos tive It is tempting to speculate *it they might correspond to the cells carrying* otype of Ig or to those carrying C^3 receptor but t Ig (20) Such a d ssociat on between B cell ant n and sIg positive cells was also observed in one t ent with lymphocytic lymphoma The opposite ght also occur as in some cases of CLL and nphocytic lymphoma with a smaller number of ell ant gen than sIg pos tive lymphocytes

The B cell ant gen was found on a large number blasts obta ned on st mulation of peripheral blood nphocytes with Cowan Staphylococci a selec e B-cell mitogen (4 9 22) but it was usually not tected on the surface of normal plasma cells or asma cells from most cases of BMG It seems erefore to be a differentiation ant gen that is lost ring full maturation to Ig secret ng plasma cells he weak express on of the ant gen on some but t all myeloma cells is consistent with a less com ete d fferent at on In fact myeloma cells are own to have a more immature nuclear chromatin ructure than plasma cells from patients with BMG no M-component (10 25) It should be em hasized that in both myeloma and BMG the ajority of the bone marrow plasma cells belong to e M-component form ng clone as demonstrated y intracellular stain ng for k and l l ght chains (27) the present series the number of plasma cells elonging to other clones could be roughly esti ated from the k/l rat o to less than 5% in the myeloma cases and to 3 30% in the BMG cases Even if the assumption is made that only 70% of the Ig containing cells in BMG belong to the M component producing cell clone and that all B cell antigen positive cells observed belong to this clone the percentage of positive cells in the clone is still significantly lower than in multiple myeloma

The presence of B-cell antigen on myeloma cells has also been reported by others (3 6) using anti sera raised against CLL lymphocytes and monkey spleen B-cells respectively Normal plasma cells were not examined in these reports Others have failed to demonstrate B-cell antigen on myeloma cells using ant sera against B-cell membrane pro teins—Ia l ke antigen—(11 24) although the antigen was detected on m togen induced plasma cells (11) Although Ia l ke antigen also might be considered as a d fferent ation ant gen in the B lymphocyte series its cellular distribut on is thus d fferent from the B-cell ant gen detected by 7470 antiserum

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Electrolytes and Whole Body Potassium in Acute Leukemia

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STRACT In a consecutive series of 22 patients h acute leukemia the total body potassium was died in 18 patients on 39 occasions during relapse l remission Total body water was also de mined A control group consisting of 88 age tched healthy volunteers was also studied The ients had a significantly lower mean potassium centration, per kg body weight, per kg lean body ss and per kg water than the controls ($p<0.001$) ividually, 11 out of the 18 patients had at least value below the lower 95% confidence limit pokalemia was frequent both in the patients with (7/11) and normal (3/6) potassium per kg lean ly mass Five of 13 investigated patients showed oratory indications of secondary hyperaldoster sm, which might be partly responsible for the pokalemia Increased serum or urine levels of ozyme were found in 62% of the patients

words acute leukemia electrolytes whole body assium

a Med Scand 206 45 1979

vious studies have demonstrated that hypo- mia occurs in acute leukemia (17 23) ozyme (27) and nephrotoxic or sodium rich ibiotics (2 38) have been suggested as probable ises of the hypokalemia Other disturbances of electrolyte and water metabolism have also n described (3 14 18 21 25 39 40)

The purpose of the present paper is to study ether hypokalemia in acute leukemia is ac npanied by a potassium depletion Previously ly anecdotal information has been available con ning total body potassium in leukemia (29) Pre inary results of this study have been reported lier (19)

SUBJECTS AND METHODS

ients

enty-one patients with acute non lymphatic leukemia l one patient with acute lymphatic leukemia were studied during 1974–75 Eighteen patients were in the initial phase of leukemia 4 had been in remission and had relapsed (Table I) Electrolyte studies were not included if they had been carried out during a period with increased serum creatinine

Treatment

As initial cytostatics rubidomycin and cytosine arabinoside were given except to patients over 70 years of age who received the latter combined with thioguanine Treatment schedules have been prescribed in a previous publication (35) Patients not studied in the initial phase of disease (nos 4 5 6 and 19) had received prednisolone in addition If these combinations failed other cytostatics were used vincristine methotrexate 6-mercaptopurine and prednisolone (VAMP) cyclophosphamide vincristine cytosine arabinoside and prednisolone (COAP) and in some patients especially those 4 with acute promyelocytic leukemia a renewed trial with rubidomycin

Controls

A group of 88 apparently healthy volunteers aged 20–94 years and weighing 48–104 kg served as controls for the whole body potassium study They were divided into four subgroups male and female under and over 50 years of age

Total body potassium

The total body potassium was estimated in a whole body counter (31) by measuring the 1 46 MeV γ rays emitted by ^{40}K which forms 0 12% of naturally occurring potassium The counter was calibrated with phantoms containing KCl and an overall error of 7 2% was found for a single measurement with a reproducibility of 5 1% One measurement of ^{40}K was performed in 18 of the patients and 2 or 3 measurements in 14 All except 3 patients were measured within 2 months from admission

Body composition measurement The total body fat was estimated from an experimentally derived equation relating the subcutaneous fat thickness in healthy volunteers to the body fat (8) The body weight minus the estimated total body fat was called the lean body mass In an attempt to estimate the amount of water in the lean body mass the total body water was measured in 10 of the patients by determining tritium activity in serum 24 hours after oral administration of 100 μCi of ^3H_2O with correction for excreted tritium activity The difference between the lean

Table I *Description of the patients*

AML=acute myeloid leukemia APML=acute promyelocytic leukemia ALL=acute lymphatic leuk AMML=acute myelomonocytic leukemia n s =not studied

Pat no	Age (y)	Sex	Weight (kg)	Diagnosis	Duration of complete and partial remission (mo)	Duration of disease (mo)	Notes
1	61	♀	n s	AML	–	1	–
2	32	♀	64 6	AML	–	6	–
3	59	♂	69 7	AML	8	12	–
4*	65	♀	51 5	AML	10	15	Adynamia terminal diabetes mellitus
5*	56	♀	76 0	AML	16	23	Adynamia psychosis
6*	36	♀	80 0	AML	22	24	Arrhythmia
7	33	♂	70 2	ALL	19	23	–
8	67	♀	57 0	APML	2	6	Arrhythmia
9	43	♂	52 1	APML	4	10	Adynamia
10	40	♀	50 2	AML	2	10	Muscular pains
11	54	♂	n s	AML	–	1	Arrhythmia
12	56	♂	88 0	AMML	7	10	Hypertonia alcoholism
13	27	♂	62.5	AML	11	16	Increased intracranial pressure
14	49	♂	74 6	AML	7	10	Acromegaly hypophysectom
15	33	♀	n s	di Guglielmo	–	3	Preleukemia for 1 y
16	65	♀	59 1	AML	6	14	Tuberculoma heart failure
17	53	♀	53 0	APML	6	11	Diabetes insipidus
18	71	♀	62 2	AML	7	13	Arrhythmia
19*	53	♀	85 6	AML	10	20	Adynamia seizures
20	80	♀	n s	AL	–	1	^{32}P treated PCV in 1969
21	45	♂	80 0	AMML	–	6	Arrhythmia
22	55	♂	69 1	APML	7	11	Diabetes insipidus arrhythmia

* Not studied in the initial phase of the disease

y mass and the total body water was called the dry body mass

Total body potassium concentrations The total body potassium was expressed per kg of body weight and of the body compartments lean body mass dry lean body mass and total body water To facilitate the statistical analysis all individual values were expressed as per cent of the mean control value for the corresponding age and sex group

Serum and urinary electrolytes and lysozymes Serum and urinary potassium and sodium concentrations determined by Technicon Flame Photometry at the tral Laboratory The normal ranges for potassium g this laboratory are 3 5–4 9 mmol/l in serum and 3 mmol in 24-hour urine and for sodium 137–145 serum Arbitrarily in order to estimate the freque hypokalemia conservatively borderline hypokalem not called hypokalemia and only potassium values l 3 2 mmol/l serum were considered as evide hypokalemia Serum concentrations of zinc magn

Table II *Potassium concentration in different body compartments in controls (mean±S D)*

	No of subj	Potassium concentration (mmol/kg) Per body weight	Per lean body weight	Per dry lean body mass	Per total body water
Males					
Under 50 y	25	51 4± 5 9	64 2±5 4	276 2±60 6	86 2± 9 2
Over 50 y	21	38 9±10 0	63 2±7 7	273 7±57 5	80 6±11 8
Females					
Under 50 y	29	43 7± 5 4	56 2±6 9	237 9±42 5	77 2±10 2
Over 50 y	13	36 3±9 0	52 7±6 6	212 3±33 0	74 4± 6 1

le III In t l eas re e t of total p t ss i as per cent f correspo d control n ean

	K/kg body we ght	K/kg lean body mass	K/kg dry lean body mass	K/kg total body water
	87	86	56	100
	88	80	106	76
	80	74		
	80	88		
	98	111	83	118
	110	103		
	104	130		
	10	96		
	70	72	55	76
	78	74	8?	73
	95	81	9?	76
	71	73	59	76
	96	111		
	64	58	6?	54
	8	111		
	64	78		
	7?	77	61	79
	86	68	70	70
	84 8	87 3	7? 6	79 8
	+13 5	+19 0	+17 4	+17 4
of pats	18	18	10	10

alc um were measured by atom c absorpt on meas ents w th the Perk n Elmer 303 and 403 apparatus ct ely The normal ranges of the laboratory are 5 μmol/l 0 72–0 90 mmol/l ? 20–2 60 mmol/l respec

Lysozyme in serum and urine was measured by a metric method (26) reported to g ve normal values of 5 mg/100 ml in serum and under 0 2 mg/100 ml ine In a few cases lysozyme was measured by a cup method (16) giv ng normal values of 4–14 μg hen h te lysozyme (HEWL)/m n serum and of 0–0 ? μg L/ml n urine Normal range for serum album n s g/l

rmone assa s Urinary excret ons of aldosterone and n concentra ons of ren n were de erm ned n 13 of ents by the Endocrinology Laboratory Ren n was m ned n fast ng pa ents n the morn ng by a New and Nuclear Rad o mmune Assay K t Aldosterone determ ned by a rad o mmune assay method (34) nal values for ren n act v ty were 0 5–1 5 ng/ml/hour e p one pos on Normal urinary aldosterone excre was 5–17 μg/24 hours The values were nterpreted n on o urinary exc et on of sod um and potass um

RESULTS

l bod potass

results from the total body potass um meas nents are g ven in Table II for the controls and able III for the leukemia pat ents The mean entrat on was s gnif cantly lower in the pat ents in the controls ($p<0\ 001$) Th s was true for potass um per kg body weight per kg lean body mass per kg dry lean body mass and per kg water The relat ve potass um def c t per kg dry lean body mass in the whole group was ?7% of the control value Eleven of the 18 pat ents stud ed had de creased potassium per kg lean body mass on one occas on Individual potass um def c t was found in 6 of 18 patients in whom the potassium per kg lean body mass was under the 95% conf dence l mit of *the controls Th s frequency is h ghly sign f cant* ($p<0\ 001$) Repeated measurements were per formed in 14 pat ents 5 of whom showed a s gnifi cant change in their total body potassium concentra t on—? from a normal to a low and 3 from a low to a normal value One patient (no 8) had a statist cally s gn f cant ncrease in potass um per kg lean body mass

Ser n electrol tes

Twelve of the 2? pat ents had interm ttent hy pokalem a Two of these 1? pat ents had less than 3 0 mmol/l for over 3 weeks 6 of the pat ents had hypokalem a on adm ssion before any treatment had been given Serum magnes um was decreased interm ttently in 8 of ?0 pat ents serum calc um n 15 of 20 serum zinc n 13 of 17 and serum sod um in 13 of 21 Two patients had hypermagnesem a Al kalos s was found interm ttently n 9 of the ?? pa

Table IV *Total body potassium in relation to stage of disease (A) treatment and hypokalemia (B)*

Potassium per kg lean body mass	Relapse	Complete and partial remission
A *Samples (n=39)*		
Normal (n=20)	12 (60 %)	8 (40 %)
Increased (n=1)	1	
Decreased (n=18)	13 (72 %)	5 (28 %)
	Cytostatic courses until 1st measurement (Mean and range)	Hypokalemia
B *Patients (n=18)*		
Normal (n=6)	4 (0–15)	3 (50 %)
Increased (n=1)	2	–
Decreased (n=11)	5 (0-16)	7 (64 %)

tients The individual means for serum albumin in 21/22 patients ranged between 25 and 41 g/l

Hormone assays and urinary electrolytes

Aldosterone in urine and/or renin in plasma was increased in 8 of 13 patients Increased values varied between 5 0 and 12 1 ng/ml/hour for renin and between 8 4 and 57 8 µg/24-hour urine for aldosterone Five of the 8 patients had hypokalemia while 3 had normal serum potassium despite increased serum aldosterone or renin In 7 patients with hypokalemia no hormone assays were available The urinary Na/K ratio was pathological (<1 0) in 7/12 hypokalemic and 3/10 normokalemic patients while the mean urinary potassium excretion was normal in the normokalemic patients The individual mean value exceeded 57 mmol/24 hours for each hypokalemic patient Four of the patients had mean values exceeding 100 mmol/24 hours despite hypokalemia

Lysozyme

The lysozyme values were increased in 13 of 21 patients Of the 13 patients with high values 8 had decreased serum potassium Four patients had normal lysozyme values despite a low serum potassium

Relations between whole body potassium and other clinical data

Table IV presents some relations between clinical data and potassium per kg lean body mass Among the 11 patients with decreased total body potassium 7 had intermittent hypokalemia but onl[y] these had hypokalemia at the time of the me[asure]ment

However when all whole body potassium m[eas]urements were taken into account there w[as no] statistical difference either between the whole[-body] potassium in relapse and remission or betwe[en the] first and the last measurement Neither coul[d a] correlation be found in the whole group betwe[en the] percentage of blasts or the WBC in the per[ipheral] blood and the total body potassium The amo[unt of] cytostatics given was not higher in the potas[sium] depleted patients than in those with a normal [potas]sium per kg lean body mass (Table IV) Fo[r pa]tients not studied in the initial phase of d[isease] had a decreased whole body potassium va[lue in] 7 of 10 measurements while the corresp[onding] figure for the others was 12 out of 29 me[asure]ments

DISCUSSION

The various methods for estimating lean bod[y mass] have been compared recently (13) The anthropometric techniques for estimating lea[n body] mass the skinfold technique and the more so[phisti]cated determination of the total body wate[r] yielded comparable results for controls a[nd pa]tients According to Delwaide (12) the clini[cal use] of total body potassium is limited by its wide range and therefore it is preferable to co[mpare] groups of patients rather than individuals

Considerable problems in evaluation o[f] body potassium values are the errors of m[easure]ments and the biological variations The m[ost dif]ficult problem is that of comparing potassium lean body mass in patients with that in co[ntrols] The significantly decreased total body pot[assium] values might be due to a changed body compo[sition] The comparison becomes invalid if for ins[tance] differences in the hydration of the lean body exist However the results of total body wat[er and] fat show comparable figures in the patients a[nd] controls Moreover the body weights of th[e pa]tients were within normal range

Some of our patients had a previous hist[ory of] diseases possibly associated with disturban[ces of] potassium metabolism (Table I) such as hy[perten]sion acromegaly (1) and alcohol abuse ever some recent reports claim that there significant decrease in total body potassium d[uring] diuretic therapy of hypertension (37) and som

s even maintain that potassium supplementa is unnecessary (11) Similarly no cirrhosis of liver was revealed at autopsy in the patient with holic abuse and potassium depletion without nosis is not reported in alcoholics For these ons and because it was considered valuable to a consecutive series of patients these patients e included in the study The only ones excluded m total potassium measurement) were patients l and 20 who either died prematurely and pa t 15 who had been given isotopes making the ssium study impossible

ompared with the controls the patients had a ificantly lower value of potassium per kg lean y mass Thus hypokalemia which has been onstrated in acute leukemia (17) is accompa by a decrease in the total body potassium But present results confirm the findings of other rts that there is no simple relationship between le body and serum potassium (7)

ome of our patients showed a significant in se in total body potassium thus suggesting that potassium depletion is reversible a finding that firms similar findings by Delwaide (12) The ors responsible for hypokalemia and potassium etion in leukemia cannot yet be completely tified Our data suggest a potassium loss in the ority of patients with a low potassium value per an body mass The single case with increased le body potassium could like a previous case be explained by the hypothesis that there is an cellular redistribution of potassium in leukemia h accounts for the hypokalemia (24) and a increase of the total potassium due to netry efficiency following the redistribution ies are in progress to elucidate the latter r

veral authors have reported altered cell mem le potentials and increased intracellular levels of um both in patients with potassium depletion and with malignant disease and uremia (4 6 10

elt (36) introduced the concept sick cell drome to integrate the different findings in cells n severely ill patients He found high intracellu evels of sodium in erythrocytes of patients with ignant disease By studying the ouabain sensi part of the cell membrane pump he found a ect which could explain the phenomenon Mir et (22) confirmed this finding interestingly in cemic subjects In addition they found evidence for a serum factor in acute leukemia which influ enced the activity of the ouabain sensitive pump The sick cell concept might be generalized to other cells in the body besides the erythrocytes on which the original studies were made (36) Besides the membrane function of potassium its metabolic aspect must also be considered Scribner and Burnell (33) using the concept potassium capaci ty emphasized the metabolic role of potassium in the cells Further studies are necessary to see whether these theories are applicable to leukemic patients

The results show that there are other electrolyte disturbances besides hypokalemia in leukemia as reported by others (14 17 21 39 40) Vincristine and cyclophosphamide are known to influence the sodium levels in serum (9 21) but hyponatremia without known cause is also reported in leukemia (25) Magnesium is affected by secondary hyper aldosteronism which was found in some of the patients and there is a relationship between magnesium depletion and hypokalcemia (30) In the investigation of this spectrum of electrolyte dis turbances the possibility of multiple primary tumors which might be endocrine must be con sidered at least in lymphatic malignancies (20) Also leukemic infiltration or coagulation disorders might damage endocrine organs such as the pituitary (3 32)

Ectopic hormone production (28 39) in ma lignancy and leukemia must be discriminated from multiple primary tumors with endocrine activity (20) In a situation where the remission frequency in leukemia is improving (15) and where progress is being made in fighting septicemia and bleeding the traditional causes of death in leukemia decreased whole body potassium and electrolyte disturbances may become clinically relevant

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Self-Poisoning Treated in the ICU

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TRACT This retrospective study compares ber and type of self poisonings admitted to the isive care units (ICU) at Sahlgren s Hospital, ienburg, during 1972 and 1976 The total ber of patients requiring intensive care was un ged but a change in the pattern of self poisoning seen In 1976 the number of patients requiring isive care following acute alcohol intoxication increased, whereas the number of barbiturate methaqualone poisonings decreased Tricyclic lepressants formed the largest group in both Fewer patients needed endotracheal intubation IPPV in 1976 than in 1972 Also, fewer complica were seen and the death rate among ICU-ed patients decreased In the Gothenburg area iturates accounted for one half of all deaths due lf poisoning and tricyclic antidepressants for one Any expected decrease in intensive care as a t of fewer barbiturate and methaqualone poison was obscured by an increase in severe alcohol ication

ords self poisoning intensive care drug pattern lity

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y cases of self poisoning admitted to hospital intensive care The object of this paper is to rt the results of a retrospective study involving poisoning treated in the intensive care units) at Sahlgren s Hospital Gothenburg during years 1972 and 1976 The number of patients itted drugs used and the time and type of ment in the ICU are evaluated

METHODS

total number of cases of self-poisoning with drugs or without alcohol or with alcohol alone was derived the admission lists of the Emergency and Accident artment for the years 1972 and 1976 Data concerning nts cared for in the ICUs were taken from the ICU rds Figures concerning the number of deaths in 1972 1976 in Gothenburg as a result of self-poisoning were from the records of the National Forensic Laboratory Gothenburg.

Principles for ICU treatment were in agreement with the so-called Scandinavian model (5 11 12) gastrointestinal lavage close observation assisted ventilation and forced diuresis when indicated

Drug were classified into one of the following groups barbiturate methaqualone other hypnotic anxiolytic analgetic tricyclic antidepressant alcohol only or other The other group included other drugs and non medicinal agents Cases of polydrug overdosage were placed into one group only where barbiturates took precedence thereafter tricyclic antidepressant methaqualone other hypnotic drugs and anxiolytic drugs in this order respectively Consequently all cases of barbiturate poisoning are shown in the figures presented but the group anxiolytic drugs in which the bensodiazepine and phenothiazines are included is underrepresented However the barbiturate and tricyclic groups are comparable since there was only one case where a barbiturate and a tricyclic antidepressant were known to have been taken together Although the barbiturate and anxiolytic groups may not directly be compared with each other we assumed that changes within these groups from 1972 to 1976 are reflected

RESULTS

Hospital admissions

The total number of hospital admissions due to deliberate self poisoning is shown in Table I Of the patients admitted 362 (15 2%) were transferred to an ICU in 1972 and 339 (11 2%) in 1976 Of patients admitted in 1972 179 were men and 183 women in 1976 168 were men and 171 women Three quarters of these patients were under the age of 40 and in both sexes there was a peak incidence in the 20s In 1976 cases of self poisoning accounted for 14 8% of patients requiring intensive care

The distribution of ingested drugs is illustrated in Fig 1 There was a considerable reduction in the proportion of self poisonings due to barbiturates and methaqualone whereas poisonings due to tricyclic antidepressants and anxiolytic drugs were equal in 1972 and 1976

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Table I *Patients admitted to the Emergency and Accident Department because of self poisoning*
Figures in parentheses indicate patients admitted to ICU

1972				1976			
2 379 (362)				2 925 (339)			
Self poisoning with/ without alcohol		Alcohol only		Self poisoning with/ without alcohol		Alcohol only	
1 516		863		1 793		1 132	
787 ♂	729 ♀	759 ♂	104 ♀	805 ♂	988 ♀	962 ♂	170 ♀

The number of patients cared for in the ICU because of alcohol intoxication only rose from 18 (5%) in 1972 to 47 (13 9%) in 1976 Likewise the number of patients taking alcohol together with a drug rose from 70 (19 3%) in 1972 to 97 (28 6%) in 1976 Polydrug overdosage occurred in 186 (51 4%) of patients in 1972 and 172 (50 7%) in 1976

In the barbiturate group there was an equal distribution between the sexes in both years studied whereas females strongly predominated in the tricyclic antidepressant group

Observation times are given in Table II Fewer patients needed intubating in 1976 than in 1972 and likewise fewer patients required assisted ventilation However of those requiring assisted ventilation the time spent on the ventilator was about the same in 1972 and 1976

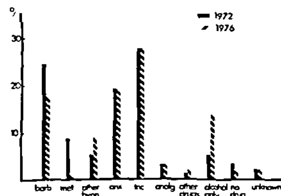


Fig 1 Self poisonings admitted to ICU expressed as % of total admissions in 1972 and 1976 *Barb* = barbiturate *met* = methaqualone *other hypn* = other hypnotic *tric* = tricyclic antidepressant *anx* = anxiolytica *analg* = analgetic No drug includes poisonings from non medicinal agents

Aspiration occurred in 7 7% of patient and 3 2% in 1976 usually before arrival at Pressure necrosis was seen in a few patie ing late Malignant cardiac arrhythmias self poisoning with tricyclic antidepressa rare

Deaths

In 1972 10 patients (2 8%) and in 1976 · (1 2%) admitted to an ICU died of self The drugs taken are listed in Table III

In the Gothenburg area a total of 70 de self poisoning were registered in 1972 ε 1976 Barbiturates accounted for almos deaths in both years and tricyclic for about a fifth (Table IV) A commonly analgetic and sedative preparation contai tylsalicylic acid dextropropoxyphene and turate accounted for 13 deaths (18 6%) in 9 deaths (15 8%) in 1976

Table II *Observation times intubation sisted ventilation in the ICU*

	1972
Mean observation time (h)	
All patients	30 0
Barbiturate group	43 0
Tricyclic antidepressant group	24 1
Patients requiring endotracheal intubation (%)	46 1
Patients requiring assisted ventilation (%)	18.5
Mean assisted ventilation time (h)	29 5

e III *Number of fatal self poisonings treated c ICU and agents taken*

	1972	1976
iturate	4	–
/clic anti ressant	1	2
olytic orprothixene)	1	1*
getic	1	–
strial alcohol	1	–
ral hydrate	1	–
1own	1	1

*ether with glutethimide

Table IV *Number of deaths in Gothenburg in 1972 and 1976 due to self poisoning with barbiturates tricyclic antidepressants and dextropropoxyphene*

	No ♂	No ♀	% of all deaths	Mean age (y)
Barbiturate				
1972	18	17	48 6	44 9
1976	14	12	45 6	46 2
Tricyclic anti depressant				
1972	5	8	18 6	33 6
1976	5	6	19 3	34 8
Dextropropoxy phene				
1972	9	4	18 6	43 7
1976	4	5	15 8	41 4

DISCUSSION

number of poisonings with drugs in the ...enburg area has increased fourfold since 1962 ...n 661 patients were admitted to this hospital ... During the same period the population of the increased from 400 000 to 500 000 inhabitants ost self poisonings are a cry for help rather i a serious suicidal attempt—it has been esti ...d that there are eight suicidal attempts for each ... h (14) Kreitman (9) concluded in 1971 that in ...ral suicide is declining while attempted suicide creasing—a statement supported by this study ...which there were about 20 attempts for each ...h Nonetheless self poisoning accounted for ... of patients treated in the ICU

...rbiturate self poisoning accounted for 60% of ...dult poisonings admitted to this hospital in ... In Matell s study of self poisoning in Stock ...1 (10) the absolute number of barbiturate ...onings remained unchanged from 1964 to 1970 ...te of an overall increase in the total number of poisonings In the present study the absolute ...iber as well as the percentage of patients taking ...biturates had declined The number of patients ...iring intensive care following methaqualone ...oning had also fallen from 1972 to 1976 This ...ld be a result of the widespread campaign ...inst the use of such drugs in the early 1970s

...elf poisoning with tricyclic antidepressants was ... largest group treated in the ICU In our materi ... women predominate in a 2 1 ratio when both ...rs are taken together Other workers have found ...redominance of women among hospital admis ...is irrespective of the agent taken (2 6 15)

The increase in alcohol intoxications probably ...ends on two factors Firstly cases of severe alcohol intoxication are now probably more often taken to a hospital than to a police arrest Secondly there may be an overall increase in alcohol abuse

The incidence of polydrug overdosage in this study—over 50% for both years studied—is higher than that reported in earlier studies (8) but in agree ment with a more recent study (6) In the latter study 24% of patients had taken alcohol together with a medicinal agent The corresponding figures in our study increased from 19 3% in 1972 to 28 6% in 1976

Changes in the pattern of drugs used with fewer barbiturate and methaqualone self poisonings re sulted in fewer patients requiring endotracheal in tubation and assisted ventilation although our treatment policy remained unchanged over the period studied Proudfoot and Park (13) also found a decrease in barbiturate poisonings but no corre sponding decrease in the need for ventilatory assis tance A reduction in the total observation time required in the ICU may have been expected with respect to the change in the pattern of drugs used However in 1976 patients were transferred from the ICU directly to a psychiatric ward whereas in 1972 patients were moved to a medical ward prior to psychiatric assessment This may also explain the increase in observation time for tricyclic antidepres sants There was a decrease in pulmonary compli cations which again can be explained by the de crease in barbiturate and methaqualone self poi sonings Earlier warnings of frequent severe ar rhythmias following tricyclic antidepressant poison ing (3) have not been substantiated

The decrease in deaths among ICU-treated self poisonings seemed at least in part to be due to a decrease in barbiturate poisonings However almost one half of fatal self poisonings in the Gothenburg area were in both years caused by barbiturates A similar proportion was recently reported by Johns (7) from England and Wales Despite a reduction of the number of hospital admissions due to barbiturate poisoning and of barbiturate prescriptions Johns found no corresponding reduction in the number of deaths The tricyclic antidepressants remain next to the barbiturates the largest group responsible for deaths by drug overdosage in the Gothenburg area almost a fifth of the total number of deaths

A large number of deaths were caused by self poisoning with a combination of aspirin dextropropoxyphene and barbiturate In Gothenburg this combination alone accounted for as many deaths as the tricyclic antidepressants This finding confirms earlier reports of the high toxicity of dextropropoxyphene especially in combination with alcohol (4 16 17) or barbiturates

CONCLUSIONS

Our study suggests that a reduction in barbiturate prescription results in fewer patients requiring intubation and assisted ventilation and fewer compli[illegible] a consequent reduction of intensive [illegible] costs However any such reduction was [illegible] by an increase in the number of alcohol intoxications requiring intensive care Also we hope that pointing out the danger of a combination of dextropropoxyphene with a barbiturate or alcohol will decrease the prescription of dextropropoxyphene

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Emergency Room Resuscitation of Patients with Cardiac Arrest outside Hospital

Outcome and Immediate Prognosis in 319 Patients

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1K ˜T Resuscitation was attempted in 319 brought to hospital with cardiac arrest dur 1 5-year period Primary successful results were ved in 50 patients (15 7%) Twelve patients were term survivors (3 4%) 10 of whom had normal 1 function whereas 2 had mild cerebral dysfunc To improve prognostication in patients with lly successful resuscitation, Bayes' theorem was ied using 4 clinical findings after 24 hours ment reactions to painful stimuli pupillary size reactions and BP Bayes theorem as well as 1 depth after 24 hours gave valuable information ding individual prognosis

words cardiac arrest resuscitation prognosis s theorem

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ntion of cardiac arrest occurring outside itals has proved difficult Attempts have been to increase survival by the use of specialized ulances which rapidly can assist the patient at ite of the accident (1 8 14 17) However in y places such ambulance systems are not lable and patients with cardiac arrest are ight to hospital by ordinary ambulances for scitation Due to the long delay before restitu of the circulation under these circumstances hances of survival are usually poor (9 10)

e have studied the results of resuscitation in an rgency room of patients with cardiac arrest oc ing outside hospital during a five year period resuscitation of patients with long standing ar will often lead to permanent brain damage in e of adequate circulation early prognostication hese cases would be of great value Therefore also attempted to find parameters of prognostic ie to improve clinical decision making

PATIENTS AND METHODS

During the period July 1 1972–June 30 1977 resuscitation was attempted in 319 patients in the emergency room at Serafimerlasarettet in Stockholm Resuscitation was started when the preliminary history indicated that the time of arrest had been short i e approximately less than 15 min Before during and after the resuscitation notes were made on parameters such as cardiac rhythm *neurological status breathing pattern* blood pressure (BP) etc Patients who after the resuscitation had palpable pulse BP and adequate peripheral circulation were taken to the intensive care unit (ICU) for respirator treatment All patients received cortisone and were hyperventilated to reduce cerebral oedema

Bayes theorem was used to calculate the probability of fatal outcome on the basis of available clinical and labora tory data during the first 24 hours The probability of a given patient having a certain outcome can be estimated by this theorem which in the medical context enables the known frequency of indicants (information from history clinical features and special investigations) in a disease to be used for diagnostic calculations χ^2 test with Yates correction was used for comparing differences between patient groups

RESULTS

Resuscitation was unsuccessful in 269 (84%) of the 319 patients and these patients were not further studied In 50 patients (15 women and 35 men) stable circulation was achieved and they were transferred to the ICU Altogether 38 hospital deaths occurred among these 50 patients 16 in the ICU and 22 in general medical wards (short term survivors) Eleven patients were discharged alive from hospital (long term survivors) One additional

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Abbreviations ICU=intensive care unit CCU=coronary care unit VF=ventricular fibrillation BP=blood pressure

Table I *ECG pupillary size and pupillary reaction to light on admission in 50 resuscitated patien*

	Grade of pupillary dilatation			Pupillary reaction to light			Initial ECG	
	Max	Normal	Unknown	Pos	Neg	Unknown	VF	Asy agonal
Long term survivors ($n=12$)	5	4	3	5	5	2	10	2
Short term survivors ($n=38$)	28	10	0	5	30	3	15	23
Significance of difference	N S			N S			$p<0.05$	

patient who was mobilized without residual cerebral dysfunction but died of reinfarction two days before planned discharge is also included among the long term survivors There was no difference in age between long and short term survivors (67 0±11 8 and 67 6±7 5 years respectively) Thus 3 4% of the 319 patients admitted with cardiac arrest survived to leave hospital Among the long term survivors 10 were without any intellectual impairment while two had mild cerebral dysfunction

Time factors

Estimations of the interval between onset of cardiac arrest and the beginning of cardiopulmonary resuscitation outside hospital were available for 8 of the 12 long term survivors and for 26 of the 38 short term survivors The mean interval in the latter group was 6±4 min and 2±2 min in the former ($p<0.05$) In contrast there was no difference between long and short term survivors as regards the

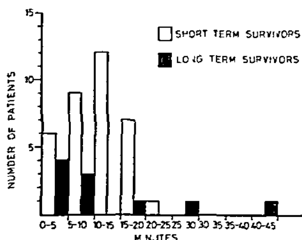


Fig 1 Interval between onset of cardiac arrest and arrival at the emergency room in 50 successfully resuscitated patients Note that two long term survivours have a very long delay

interval between onset of cardiac arrest sion to hospital Three long term survivo very long delays (20 28 and 45 min respect but in all these cases medically trained perso been near by and immediately started cardia sage and artificial ventilation (Fig 1)

Hospital course of primary successful resuscitations

Pupillary light reactions and size on admi not differ among long and short term (Table I) Three of the long term survi fixed dilated pupils Ten long term and term survivors had ventricular fibrillation admission ($p<0.05$) Ten of 25 patients with 2 of 19 with asystole or agonal rhythms sion could later be discharged (N S) There difference in assessed time of circulatory a tween patients with VF or asystole on ad Spontaneous respiration recurred sign more often among long term than sh survivors immediately after successful resu ($p<0.05$) Hypotension (BP<90 mmHg circulation was restored was seen in survivors only (Table II) Twenty four ho successful resuscitation all long term surviv normal pupillary reactions normal respo painful stimuli and normal BP None of the still in coma after 24 hours could be di while 12 of 13 non-comatose patients we term survivors (Table III) The diagnoses in Table IV In the majority of the patie underlying cause of cardiac arrest was my *infarction An unsuspected high frequency c* brovascular lesions (7/30) was found in t topsied cases

Prognostic model

The probability of a fatal outcome in all resus patients (prior probability) was 38/50 i e 0 7

le II *Pupillary size and light reaction BP and breathing pattern immediately following resuscitation in ... ton to survival*

	Grade of pupillary reaction			Pupillary light reaction			Systolic BP (mmHg)			Spontaneous breathing		
	Max	Normal	Unknown	Pos	Neg	Unknown	≥90	<90	Unknown	Present	Absent	Unknown
...g term survivors ... 12)	1	11	0	9	2	1	11	0	1	10	2	0
...t term survivors ... 38)	8	28	2	21	12	5	24	11	3	14	23	1
...ificance ... difference	N S			N S			N S			$p<0.05$		

...culation was repeated for new indicants and a ...ditioned probability was constructed The prob...ity of survival/fatal outcome was calculated ... four items of information (indicants)—reac...s to painful stimuli pupillary light reaction and ... and BP 24 hours after resuscitation These ...cants were chosen because they appeared to ...e predictive power *Example* A patient has the ...owing physical signs 24 hours after resuscitation ...otension fixed dilated pupils and no reaction to ...inful stimuli The probability of fatal outcome ...ived from Bayes theorem is 0 999 Another ...ient is normotensive (BP>90 mmHg) has nor...l pupillary light reaction and size and adequate ...ponse to painful stimuli The probability of fatal ...come is 0 27 i e the likelihood of survival is ...

DISCUSSION

...w reports regarding resuscitation in emergency ...ms have been published while experience of resuscitation of patients already admitted to hospital and in mobile coronary care units (CCU) is well documented (1 8 14 17 18) In one series from Oslo four (5%) of 76 patients resuscitated in an emergency room after cardiac arrest outside hospital could be discharged (9) Seven (8%) of 84 admitted patients could be discharged in another series from Copenhagen (10) In that study nearly 50% of the patients had asystole on admission and none of these survived to leave the hospital The results from our study as well as those from CCUs or mobile CCUs are in agreement with these findings (10 13 17) Patients with VF may be thought to have a shorter delay prior to resuscitation but we did not find any significant trend to support this supposition The difference in prognosis between patients with asystole and VF may also have an additional explanation VF may occur without major myocardial damage as distinguished from asystole which more commonly may be secondary to extensive septal damage with resultant complete heart

...ble III *Pupillary size and light reaction pain reaction and BP in relation to survival 24 hours after ...esuscitation*

	Grade of pupillary dilatation			Pupillary light reaction			Systolic BP (mmHg)			Reaction to painful stimuli		
	Max	Normal	Unknown	Pos	Neg	Unknown	>90	<90	Unknown	Pos	Neg	Unknown
...ng term survivors ...=12)	0	12	0	12	0	0	12	0	0	12	0	0
...ort term survivors ...=38)	8	26	4	14	20	4	25	8	5	11	20	7
...nificance ...f difference	N S			$p<0.01$			N S			$p<0.001$		

Table IV Diagnoses in 50 resuscitated patients

Short term survivors[a] (n=38)		Long term survivors (n=12)	
Myocardial infarction		Myocardial infarction	
Recent	6	Recent	2
Old	2	Suspected	5
Recent and old	14	Primary VF	4
Stroke	3	Drowning	1
Subarachnoidal bleeding	4		
Pulmonary embolus	1		
Unknown	8		

[a] 30 patients autopsied

block Furthermore the VF may have been preceded by ventricular tachycardia giving some but inadequate circulation

The clinician concerned with the management of patients in coma after resuscitation often has to consider how long to persist with life supporting measures His dilemma at one stage is to decide between full intensive care with artificial ventilation proper correction of fluid balance etc and the alternative i e ventilation must be discontinued because of apparent fatal prognosis These decisions depend on his ability to predict the course and outcome which in turn involves an evaluation and integration of clinical findings and a variety of investigations Without any factual base such decisions may be hazardous Furthermore the situation may be complicated if the physician has limited resources of intensive care at his disposal In our study 115 respirator days during five years were used for patients who later succumbed If accurate predictions of the outcome could be decided one day after resuscitation 89 days in the ICU could have been reallocated The discriminatory power of Bayes theorem on our patients seemed no better than the depth of coma after 24 hours treatment However added to the observation of the coma depth it could give further valuable indication of the individual prognosis

During the last decade several studies have evaluated the predictive value of individual factors in patients with coma (7 11 12 20 21) A review of the literature with respect to prognosis after cardiac arrest and coma in view of our own results gives the following conclusions

1 Coma per se after cardiac arrest is an unfavourable sign In a series of 284 resuscitated patients with cardiac arrest Bell and Hodgson (2) reported that only 19% of comatose patients lived to be discharged from hospital compared with 5[?] non comatose patients

2 The duration of the postanoxic coma is a[?] ful prognostic sign Bokonjic and Buchthal (4) f[?] that clinical recovery was complete in 90% of patients who had been comatose for less tha[?] hours In our series 12 of 13 patients in com[?] less than 24 hours lived to be discharged Altho[?] the majority of reports of prognosis after posta[?]ic coma postulates that 2–3 days with pers[?] coma usually indicates a fatal outcome there[?] exceptions Norris and Chandraskekar (16) [?]ported a patient with coma persisting for five [?] after cardiac arrest due to a myocardial infa[?] with VF in whom no residual intellectual or f[?]tional impairment was present 6 months later

3 Age has no relation to the outcome In the[?] patients in medical coma reported by Caronna[?] (6) age had no predictive value which is in a[?]ment with our findings All our long term surv[?] above 75 years of age were discharged without[?] sign of impaired brain function

4 The electroencephalogram appears to b[?] accurate predictor of outcome (3 15 19) bu[?] unacceptable frequency of false positive re[?] has been reported (19) Furthermore it is a la[?]ous and time-consuming procedure not al[?] available in routine care

5 The prognostic value of neurological signs[?] been evaluated in several reports (6 7 12 21) T[?] neurological signs may have potential pred[?] value the oculovestibular response and th[?]sponse to painful stimuli Caronna and Plum[?] found that an absent oculovestibular response[?] ways implied severe disability or death Willoug[?] and Leach (21) reported that patients in coma a[?] cardiac arrest who were unresponsive or[?]sponded in a reflex fashion to painful stim[?]

d or survived with intellectual damage In our ~es all long term survivors responded normally — pa nful stimuli wh le 20 of 38 short term vivors had an abnormal reaction 24 hours after diac arrest An important observation is that the ical state of motor decerebration may be re s ble if the corneal and deep tendon reflexes are ict and if hypotension is absent (5) Caronna et (6) found that the oculovestibular reflexes gave best s ngle pred ction 93% of their pat ents h absent oculovestibular reflexes subsequently d A combination of oculovestibular reflexes and motor response to noxious stimulat on added the predict ve power Non reactive pup ls on nission or immediately after successful resusci on gave no further informat on of prognostic ue in our series However persistent fixed p ls 24 hours after resuscitation appeared to be an ificant of fatal outcome

Resumption of spontaneous respirat on im diately after resuscitation appears to be of pre tive value Ten of 12 long term survivors in our ies resumed spontaneous respiration compared 14 of 38 short term survivors

The results from our study show that approxi tely 4% of all patients admitted to an emergency om will be long term survivors One of four pa its with initially successful resuscitation will vive In order to avoid unnecessary treatment in Js however we need better methods of prog tication in these patients

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Work Status after Coronary Bypass Surgery

A Prospective Randomized Study with Ergometric and Angiographic Correlations

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STRACT The rate of return to work was assessed i series of patients with coronary heart disease domly allocated to medical and surgical treatment ups of 50 patients each *Sixteen of the medical and* of the surgical patients were already retired at y and did not resume work later Only 9 patients %) on medical therapy were working at 2 year ow up in contrast to 18 (60%) working after ass surgery ($p<0.05$) Functional classification of ina pectoris and exercise tolerance on ergometry e significantly better in the surgical group, espe ly in the surgical subgroup at work Repeated toperative angiographies of the inserted grafts native vessels disclosed that completeness of ascularization was related to work status after ass surgery The data suggest that a combination oronary bypass surgery and medical therapy n indicated is superior to medical therapy alone nfluencing the rate of working in coronary heart ase

*words coronary heart disease coronary angio-*hy exercise testing

a Med Scand 206 61 1979

ronary bypass surgery results in marked relief of nptoms in the majority of patients (3 12) This proved quality of life should affect the rate of urn to work However the non randomized dies that have addressed themselves to this prob 1 (1 2 8 10 11 13 16) have shown that despite viation of *symptoms fewer patients than ex* ted have resumed work the proportion ranging m 40 to about 80% The motivation to return to rk is evidently related to a number of considera ns including the physician s attitude and the nerosity of disability programs which differ from * community to another It is therefore not relevant to judge the return to work after bypass surgery without the analysis of a concomitant randomized group subjected only to medical therapy

We report the rate of return to work after coronary bypass surgery in a randomized series followed prospectively

PATIENTS AND METHODS

One hundred male patients under the age of 65 were randomly allocated into two groups of 50 each The criteria for inclusion and exclusion as well as the randomization process have been reported earlier (15) The basic requirements were angina pectoris which did not respond satisfactorily to medical therapy including β blockade and short and long acting nitrates at least a 2 vessel disease revealed by coronary angiography and good left ventricular function (ejection fraction $\geq 50\%$) One group received medical therapy alone the other coronary bypass surgery and medical therapy when indicated A comparison of the groups with regard to the severity of angina the preva*lence of past myocardial infarctions the degree of coro*nary atherosclerosis left ventricular function and exercise tolerance at entry did not reveal any significant differences

The severity of angina pectoris was graded as follows 1 = no angina 2 = angina when walking uphill/upstairs 3 = angina when walking rapidly on the level 4 = angina when walking slowly on the level and 5 = grade 4 + occasionally pain at rest Patients with intractable angina were not randomized Exercise testing was performed with an electrically braked bicycle ergometer up to the subjective maximum consisting of angina requiring trinitrin as earlier described (4) In a number of patients who were asymptomatic postoperatively the test was discontinued at a heart rate exceeding *85%* of the age predicted maximum In the testing at entry treatment with β blocking drugs was discontinued at least a week before the test in the subsequent testing these compounds were allowed The exercise tolerance is reported as the maximal tolerated load in kNm (=102 kpm/min)

Postoperative selective coronary angiographies were performed at 3 weeks 1 year and 5 years after the opera

Table I *Characteristics of patients working at entry*

	Medical group	Surgical group
No of pats	34	30
Physically demanding jobs	11 (32%)	13 (43%)
Age (y)*	46 3±6 9	48 5±5 7
Functional class*	3 4±0 9	3 5±0 8
Maximal load (kNm/min)*	5 6±2 1	5 8±2 2
No and % of pats on β blockers	30 (88%)	26 (87%)
Rate of retirement		
6 mo	1 dead 13 retired 20 at work	8 retired 22 at work
12 mo	3 dead 18 retired 13 at work	10 retired 20 at work
24 mo	4 dead 21 retired 9 at work	12 retired 18 at work

Mean ± S D of the mean

tion Both the grafts and the native vessels were injected to assess the progression of disease in the coronary arteries (5) Completeness of revascularization was deemed to exist if 1) all significant (≥50%) lesions were bypassed 2) none of the grafts were occluded 3) no new significant lesions developed in the unbypassed arteries 4) no new significant lesions developed distal to graft anastomosis The medical group was first subjected to repeated angiography after 5 years follow up

The patients were studied clinically and with exercise testing at 6-month and 1 year follow up and annually thereafter The follow up times range from 2 to 5 years with a 100% follow up at 2 years which forms the cut off point of this report

RESULTS

At entry into the trial 16 patients in the medical group and 19 in the surgical group were permanently retired One patient in the surgical group refused to undergo the operation This left 34 patients in the medical and 30 in the surgical group to be followed with regard to work status None of the patients retired at entry resumed work later There were no significant differences in the characteristics of the medical and surgical groups (Table I) As is evident from Table I there was no peroperative or postoperative mortality in the surgical group whereas 4 patients (12%) died in the medical group during the follow up At 2 years 9 (26%) of 34 medical patients were working in contrast (60%) of 30 surgical patients (Fig 1) If the are included the difference is significant at t level (χ^2=6 035) if the deaths are exclud significant at the 5% level (χ^2=4 304) I groups the work status was dichotomi e en or retirement without a clear trend to pa employment or a change to less demanding j

The characteristics of the relevant subgro given in Table II The only significant differ the medical group was the better functional c the patients at work In the surgical group tients at work were some 4 years younger an maximal tolerated load c 70% higher than the retired patients The surgical group had overall functional classification the retired s patients differed significantly from the reti cal patients (t=3 473 p<0 001) but not medical patients at work the surgical work differed significantly from both the medical patients (t=6 810 p<0 001) and cal patients at work (t=3 125 p<0 01) Th applied to the maximal load of the surgical at work whereas the mean maximal load retired surgical patients was almost the same of the retired medical patients

Repeated coronary angiography in the group revealed that only 3 (25%) of the 12

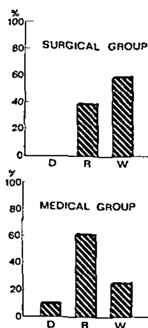


Fig 1 Proportions of patients deceased (*D*) retir and working (*W*) after 2 years follow up

Table II. *Characteristics of the study groups at 2 year follow up*

	Medical group			Surgical group		
	Retired (n=21)	At work (n=9)	p	Retired (n=12)	At work (n=18)	p
ically demanding jobs	9 (43%)	2 (22%)	ns	7 (58%)	6 (33%)	ns
(y)	46.7±4.7*	48.0±9.0	ns	47.9±5.3	43.5±4.8	<0.05
tional class*	3.7±0.7	2.8±0.7	<0.01	2.3±1.3	1.8±1.0	ns
imal load (kNm/min)	5.5±2.3	6.6±2.9	ns	5.3±2.9	8.9±2.4	<0.001
and % of pats on β blockers	21 (100%)	8 (89%)	ns	5 (42%)	12 (67%)	ns

an ± S.D. of the mean.
Not significant ($p>0.05$).

…nts were completely revascularized whereas …57%) of the 18 patients at work exhibited complete revascularization ($\chi^2=4.185$, $p<0.05$).

DISCUSSION

…weakness is easily discernible in our study—small sample size. However, its impact on the …lity of the data would appear only if the com…tion of the series deviates considerably from the …ulation at large. When the present study was …ed in 1973 and for some years thereafter our …tution was the only one in Finland performing …nary bypass surgery. This meant that we re…d patients from the whole country including …ers and lumberjacks engaged in heavy manual …

The proportion of patients in physically de…ding jobs is fairly high (Table I), the surgical … exhibiting a prevalence some 10% higher … the medical group. This excludes the pos…ty that the significantly higher rate of return to … after coronary bypass surgery could be due to …ness in the distribution of occupations.

…e functional classification of angina based on …patients' own testimony is prone to inaccuracy. …e present study the functional classes of the …rent subgroups (Table II) were nicely paral…l by the data on exercise testing, which clearly …ved the superiority of the surgical subgroup at … It should be noted, however, that a fairly high …ortion of the surgical patients were on β block… drugs because of residual angina, arrhythmias, …rtension or combinations of these. According …he difference observed in the rate of return to …k and in other factors reflects the effect of …ass surgery, and additional medical therapy … n indicated, over medical therapy alone.

The motivation to work with manifest coronary heart disease is related to a number of variables: physical, emotional and socioeconomic. It is anticipated that these are evenly distributed in a series with random design. This might not be true, however, since the medical subset is deprived of the currently fashionable mode of surgical therapy and this may adversely affect the emotional components of work motivation. This factor may be operative in the present study since the retired medical patients had a significantly poorer functional classification than the retired surgical patients despite similar exercise tolerance on ergometry (Table II). The anatomical substrate for the difference in the subjective and objective exercise tolerance between the two surgical subgroups was evidently the degree of revascularization. Both groups share the other potential factors evoking pain relief, e.g. the placebo effect, pericoronary denervation, etc. (3). The completeness of the revascularization was assessed on the basis of findings at two postoperative angiographies but not exactly at 2 years after the operation. There is a great deal of evidence that the majority of graft occlusions occur very early with a low rate of further attrition (4, 7, 9). The changes in native arteries may, however, develop and progress continuously (5, 6), introducing an unknown component into our series between 1 and 2 years of follow up.

Dissatisfaction can be expressed about the rate of resuming work after coronary bypass surgery. The reasons for the discrepancy between reality and expectations are certainly numerous and not least based on local socioeconomic conditions. The present study with random design clearly suggests that coronary bypass surgery coupled with medical therapy, when indicated, results in a higher rate of

working than medical therapy alone in a series of patients fulfilling the entry criteria outlined

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Mortalıty, Arrhythmıas and Pump Faılure ın Acute Myocardıal Infarctıon ın Relatıon to Estımated Infarct Sıze

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TRACT Serıal estımatıons of total serum
me kınase (S CK) were made in 194 consecutıve
ıts *with acute myocardıal ınfarctıon (AMI)* By
the maxımum CK value could not separate
ıts in terms of hıgh and low mortalıty but when
maxımum CK value was related to age for pa
with and without a history of previous AMI,
ubgroups became apparent one with 46% mor
(hıgh rısk group) and another with 6% (low
roup) durıng the hospıtal stay plus the next 90
In 114 of the patıents ınfarct sıze could be
lated A good correlatıon was found between
mum CK and calculated ınfarct sıze ($r = 0\ 93$)
lated ınfarct sıze alone could not dıstınguısh
en hıgh and low mortalıty but when it was
ed to age for patıents with and without a history
AMI, two subgroups emerged, one with
mortalıty and another with 3% durıng the hos
stay plus the next 90 days The ıncıdence of
ıcular tachycardıa durıng the stay ın the Coro-
Care Unıt dıd not dıffer between the two rısk
s separated eıther by maxımum CK value or
lated ınfarct sıze However, the ıncıdence of
and severe left heart faılure durıng the acute
was hıgher ın the hıgh rısk groups

words acute myocardıal ınfarctıon ınfarct sıze
ıne kınase prognosıs ventrıcular tachycardıa
Med Scand 206 65 1979

al determınatıons of total serum creatıne kınase
K) have been used to assess ınfarct sıze with
aıd of a computer program (19) A correlatıon
been found not only between ınfarct sıze and
talıty (22) but also between ınfarct sıze and left
trıcular functıon (10) left heart faılure (13) fre
ncy of ventrıcular arrhythmıas (17) and ven
ılar fıbrıllatıon threshold after acute myocardıal
rctıon (AMI) (2)

However, the method for calculatıng ınfarct sıze ıs complıcated and requıres a computer system that ıs not avaılable to most hospıtals Recently prelımınary results were presented for a sımpler method for estımatıng ınfarct sıze and predıctıng mortalıty rısk By combınıng the maxımum CK value obtaıned from serıal estımatıons of S-CK age of the patıent and hıstory of prevıous AMI two subgroups could be dıscerned one with 46% and *another with 6% hospıtal plus three month mortalıty* (6) In the present study that serıes of patıents has been extended and a lınear dıscrımınant analysıs has been used to separate patıents with dıfferent mortalıty rısks For comparıson ınfarct sıze has also been calculated by a computer program accordıng to Sobel et al (23) The frequency of arrhythmıas and pump faılures ın the total serıes and ın the dıfferent rısk groups has also been studıed as well as mortalıty ın relatıon to the dıfferent complıcatıons and rısk groups

PATIENTS AND METHODS

Consecutıve patıents admıtted to the Coronary Care Unıt (CCU) wıthın 48 hours after onset of symptoms consıstent with AMI were ıncluded ın the study The dıagnosıs of AMI was based on 1) appearance of a pathologıc Q wave and/or appearance or dısappearance of a localızed ST elevatıon followed by a T ınversıon and/or 2) two raısed

---

Abbrevıatıons CK = creatıne kınase S-CK = serum CK AMI = acute myocardıal ınfarctıon CCU = coronary care unıt S-ASAT = serum aspartate amınotransferase S-ALAT = serum alanıne amınotransferase ECG = electrocardıogram VT = ventrıcular tachycardıa ISO = observed ınfarct sıze

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S-ASAT (serum aspartate aminotransferase) values with a maximum about 24 hours after onset of symptoms in association with lower S ALAT (serum alanine aminotransferase) values with a maximum after about 36 hours 3) findings at autopsy of myocardial necrosis of an age corresponding to the onset of symptoms

A 12 lead electrocardiogram (ECG) was registered on admission and each morning during three days A continuous one lead ECG was monitored on an oscilloscope and recorded by an ink jet recorder as long as the patient stayed in the CCU Arrhythmias were noted in a data chart

The patients were examined clinically at least three times daily Heart rate blood pressure and respiratory rate were recorded every hour These results were also recorded in the data chart All injections in the CCU were given intravenously

Serum samples for estimation of S-ASAT and S ALAT were taken on admission at 8 a m and 8 p m daily during three days Serum samples for estimation of S-CK were taken on admission and then every two hours during the first 12 hours and every four hours during the next 12–24 hours The sample was centrifuged and the serum was frozen to −18°C for 1–3 days The CK activity expressed in mU/ml (4) was measured at 37°C with a spectrophotometric method described by Oliver (15) and modified by Rosalki (18) The relative methodological error obtained from double samples was 7% Comparison of CK activity in samples analysed immediately and after freezing showed no significant differences Only CK curves starting below an S-CK level of 400 mU/ml were accepted in the study

Definitions

Supraventricular tachyarrhythmia Onset of sinus tachycardia atrial tachycardia atrial flutter atrial fibrillation or nodal tachycardia *Supraventricular bradyarrhythmia* Onset of sinus bradycardia sinus arrest or nodal rhythm *Ventricular tachycardia (VT)* Three or more ventricular ectopic beats in succession *Hypotension* A systolic blood pressure of 90 mmHg or below *Shock* Hypotension in combination with at least three of the following criteria 1) oliguria 2) deterioration of sensorium 3) cold skin 4) cyanosis and 5) acidosis *Moderate left heart failure* Basal pulmonary crepitant rales *Severe left heart failure* Rales up to scapula or frank pulmonary oedema

CK maximum The highest value reached Fourteen curves were still rising when the sampling was discontinued These curves will be discussed separately No curves started with the maximum value

Infarct size was calculated according to Sobel et al (23) by a computer program For optimal results with this method only CK curves starting from a normal value (100 mU/ml 37°C) were accepted The calculated infarct size in accordance with Sobel et al is termed *observed infarct size* (ISO) and expressed in CK gram equivalents (CK gEq)

Statistical methods

The statistical calculations have been made with the χ^2 test with Yate s correction or Student s t test Separation

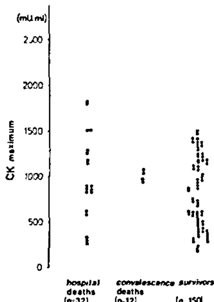


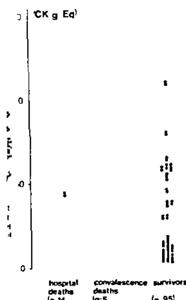
Fig 1 CK maxima for hospital deaths conv deaths (3 months) and survivors

of the risk groups was done with a linear d analysis (BMD04M Health Sciences Computing UCLA)

RESULTS

During the period of investigation 241 tients were treated in the CCU Eight patie in severe circulatory distress on admissio serum samples for estimation of S CK obtained None of them survived for more hour in the CCU A further 39 patie excluded because their CK curves started serum level of 400 mU/ml Remaining patients 139 men and 55 women aged 39- (mean 64) Fifty per cent of the patients we ted within 3 hours from onset of symptom four (33%) had a history of a previous AM ty two patients (16%) died in hospital and 12 within three months giving a combined plus three month mortality of 23% None given i m injections before admission T maximum value for S ASAT was 3 22 µkat/ S-CK 983 mU/ml

CK curves which started from a norm were found in 114 patients and these curv used to calculate the ISO These patients differ from the total series regarding age se bution history of previous AMI or enzym ma However there was a tendency toward



ISO calculated by the computer method for hospi eaths convalescence deaths (3 months) and sur s

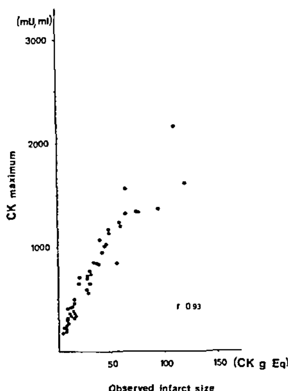


Fig 3 Correlation between CK maximum and ISO calculated by the computer method

mortality in this group although the difference not significant compared with the total series teen of the 114 patients (17%) died within three ths

g 1 shows that the CK maxima for hospital hs convalescence (three month) deaths and vivors are within the same range Fig 2 illus s the same for ISO Fig 3 shows the correla between CK maximum and ISO (r=0 93 ore 14)

is obvious from Figs 1 and 2 that neither imum CK nor ISO can be used for individual nostics of mortality However when CK xima are related to age for patients with or with a previous history of AMI discriminant ysis can separate two groups with different noses (Fig 4) For patients without a history of ious AMI the mortality in the high risk group ve the discriminating line— the risk line) is (25/27) and in the low risk group (below the line) 3% (2/73) For patients with a history of ious AMI the corresponding figures are 50% 24) and 13% (5/40) Altogether the hospital plus valescence (3 month) mortality in the high risk up is 46% (37/81) and in the low risk group 6% 13) The corresponding figures for CCU mor y are 26 vs 3% and for hospital mortality 35 vs All these differences are statistically significant 0 001)

Fig 5 illustrates the same method of separation when ISO is related to age for patients with or without a history of previous AMI For patients without a history of previous AMI the mortality in the high risk group is 39% (10/26) and in the low risk group 0% (0/47) The corresponding figures for patients with a history of previous AMI are 47 (7/15) and 8% (2/26) Altogether the mortality in the high risk group is 42% (17/41) and in the low risk group 3% (2/73) The corresponding figures for both CCU mortality and hospital mortality are 34% vs 1% All differences are statistically significant (p< 0 001)

Table I shows the total frequency of arrhythmias and pump failure and these complications in the risk groups separated by either CK maximum or ISO in combination with age and history of previous AMI Table II illustrates the mortality in relation to the different complications in these risk groups As can bee seen from the tables the results were essentially the same when CK maximum or ISO was used for separation with no statistically significant differences

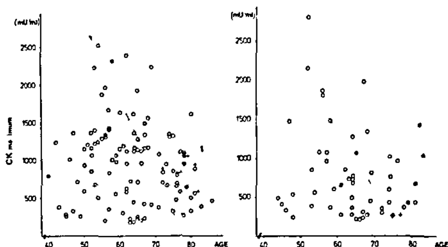


Fig 4 CK maxima in relation to age for patients (right) and without (left) history of previous AMI The discriminating lines separate the high risk (above the dotted lines) the low risk groups (below the dotted lines) O = survivors + = hospital d ⊗ = convalescence d

DISCUSSION

A small number of patients in severe circulatory distress on admission were excluded from the study which may explain the somewhat low mortality An interesting finding was the tendency towards a lower mortality in the 114 patients with CK curves starting from a normal value These patients had a tendency towards a shorter delay between the onset of symptoms and admission to the CCU which perhaps contributes to the lower mortality Apart from this the 114 patients seemed to be representative of the total material

The prognosis after an AMI seems to depend at least partly upon the mass and quality of the remaining viable myocardium In previous series a correlation has been found between on th hand enzyme maximum and on the other size and/or mortality (5 9 20 21) In the p series CK maximum or ISO alone could not individual mortality A good prediction was ever obtained when the age of the patient a history of previous AMI were included Th ence of age has in previous studies been sh be of great prognostic importance (1, 14 might be considered as a rough estimate quality of the remaining myocardium The the viable myocardium is reduced after an A accordingly a raised mortality has been r after reinfarctions (7 8) An interesting fir the present series was a difference of ab mU/ml or 25 CK gEq between the discrir

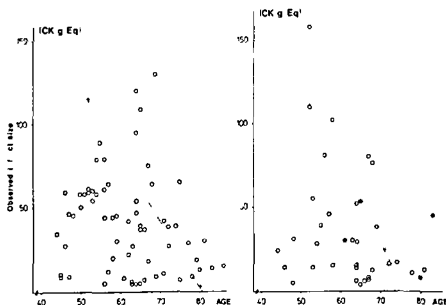


Fig 5 ISO in relation for patients with (righ without (left) a histor previous AMI The d criminating lines sepa high risk groups (abov dotted lines) from the risk groups (below the lines) Symbols as in l

I Frequency (%) of complications in the total series and in the risk groups separated by CK num or ISO

cal d fferences are calculated between h gh and low risk groups separated by CK maximum or ISO respectively

	Total		H gh risk group		Low risk group		
	CK max (n−194)	ISO (n 114)	CK max (n=81)	ISO (n 40)	CK max (n 113)	ISO (n 74)	p
ventricular tachy thmia	16	15	22	20	12	12	N S
ventricular brady thm a	9	12	10	15	9	11	N S
	41	40	48	45	36	37	N S
icular fbrillation	4	3	6	5	3	1	N S
d degree and complete block	10	7	19	15	4	1	<0 05/0 01
icular standst ll	7	5	15	13	2	1	<0 05
tens on	13	18	17	28	10	14	N S
	5	5	11	13	1	1	<0 01
rate left heart fa lure	4?	4?	46	43	39	4?	N S
e left heart failure	14	12	26	28	5	4	<0 01

aration w th CK maximum gives $p<0.05$ with ISO $p<0.01$

for patients with or without a history of previ AMI This difference might be explained by the ous myocardial damage in the former pat ents om the correlat on between CK maximum and and the almost identical separation of risk s with these parameters it was concluded that maximum can be used as an estimation of in size if the CK samples are obtained serially In an earl er series (19) a correlation coeffici f 0 8 was found between CK maximum and but that series comprised only 11 patients maximum was obtained from serial estima tions and was defined as the highest value reached However this series includes 14 curves that were still rising when the sampling was discontinued This has no influence on prognostic evaluation in the ten cases in whom the CK curves ended above the risk line separating the high and low risk groups (Fig 4) since these patients were already classified as high risk cases However the possibility of be ing erroneously classified as false low risk cases exists in the four patients whose CK curves ended below the risk line

The total frequency of complications was in ac

e II Three month mortal ty (% of patients with respective complication) in relation to d fferent l cat ons in the total series and in the risk groups separated by CK maximum or ISO

	Total		H gh risk group		Low risk group	
	CK max	ISO	CK max	ISO	CK max	ISO
aventricular tachy rythmia	39	24	67	50	0	0
aventricular brady rythm a	22	14	38	33	10	0
	?6	24	41	50	13	7
ricular fbrillat on	75	33	80	50	66	0
nd degree and complete block	55	63	67	67	20	50
tricular standstill	100	100	100	100	100	100
otension	16	38	29	64	0	10
k	90	100	89	100	100	100
erate left heart fa lure	23	19	43	41	7	6
re left heart fa lure	48	36	57	45	17	0
l material	23	17	46	43	6	3

cordance with findings of previous authors (8) Roberts et al (17) found an increasing incidence of ventricular arrhythmias with increasing infarct size calculated by the computer method Mogensen (11) found a correlation between the maximal S ASAT value and the incidence of VT Chapman (3) observed an association between the incidence of both supraventricular and ventricular arhythmias and the rise in serum transaminase levels Also in the present series patients with VT had higher CK maxima (mean 1 100 mU/ml) than those without (mean 891 mU/ml) ($p<0.05$) but the incidence of VT did not differ in the two risk groups However the mortality among patients with VT in the high risk group was significantly higher ($p<0.05$) than among patients with VT in the low risk group The figures were essentially the same when the risk groups were separated by ISO age and history Thus a VT per se was not associated with an increased mortality but if it was combined with a high CK maximum (or ISO) and/or advanced age the mortality did increase

The incidence of shock and severe left heart failure was significantly increased in the high risk groups separated either by CK maximum or ISO which is in accordance with the findings of Norris et al (13) who found an increasing incidence of left heart failure with increasing infarct size measured by the computer method Sjögren (20) also found an ...sing incidence of left heart failure with in...sing S ASAT maxima Shock and severe left heart failure were also associated with a higher mortality rate in our total series However there were too few patients with these complications in the low risk groups to permit comparison between the associated mortality in the different risk groups

Separating with both CK maximum or ISO gave a significant overrepresentation of second degree AV block complete AV block and ventricular standstill in the high risk groups These complications were also associated with an increased mortality in the total material but the numbers were to small in the low risk groups to permit further conclusions Ventricular standstill was a complicating arrhythmia in all cases with 100% mortality

There were eight cases of ventricular fibrillation evenly distributed among the high and low risk groups The mortality figures associated with this complication were essentially equal in the different risk groups, although the numbers were too small to permit conclusions

The incidences of hypotension modera... heart failure and supraventricular bradyarrh... were of the same magnitude in the di... groups The mortality associated with thes... plications did not differ from the mortality... total series Patients with supraventricula... ycardia were also evenly distributed... risk groups but the high risk patients had a... mortality than those in the low risk group... same complication

CONCLUSIONS

There was a good correlation between C... imum obtained from serial estimations of S-... ISO By themselves CK maximum or ISO w... good predictors of mortality after AMI T... bination of CK maximum (or ISO), age of... tient and history of previous AMI separa... group of patients with 46% (42%) hospi... three month mortality after AMI from... group with only 6% (3%) mortality In the h... *groups there was an overrepresentation of*... with severe left heart failure and shock in... to VT which was evenly distributed am... tients with high and low mortality risk

ACKNOWLEDGEMENT

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The Q-T Syndrome—A Family Description

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TRACT This paper describes a family of nine ıgs of whom five suffer from the surdocardiac rome All five are deaf mute and have medical ries typical of the syndrome with frequent syn l attacks during the childhood, often caused by s Two of these five siblings have not suffered than single attacks since puberty and are still The other three had had continuous frequent ks into adult years and died in connection with opes at 20, 27 and 37 years of age The diagnosis, ogenesis, treatment and genetics of the syndrome discussed

words Q T syndrome hereditary diseases electro-ography

Med Scand 206 73 1979

)57 Jervell and Lange Nielsen described a fami ıth the Q T syndrome (8) The syndrome is acterized by 1) Arrhythmias which may or not be accompanied by angina pectoris syn al attacks and death 2) A prolonged Q T inter ın the ECG 3) Familial occurrence 4) Con tal deafness (surdocardiac type)

ı 1963 two families were described both having milar syndrome but all members of which had mal hearing (Romano-Ward type) (14 15) In 2 a family with the long Q T syndrome was overed whose affected members either had mal or reduced high frequency hearing (11) en cases of the syndrome occurring in Sweden e been described in published articles but most he cases have been from different families (10) The different types of the syndrome appear to e similar genetic backgrounds with separate in ıtance of hearing and heart lesion (11) It has n surmised that the syndrome with total deaf s is inherited through an autosomal recessive chanism whilst the syndrome without deafness is inherited through an autosomal dominant mechanism

This paper describes a family consisting of nine brothers and sisters of whom five are deaf Two of these five siblings died without ECG being re corded The ECGs of the other three had clearly prolonged Q T intervals The health of the family s parental generation and of the family s offspring and their children has been investigated to a certain extent This paper is based upon anamnestic infor mation from our patient upon correspondence with his brothers and sisters and upon extracts from medical journals

CASE REPORT

Our patient (IV 8) is a man born in 1922 He is a fraternal twin and has been deaf mute since birth Both his par ents who were cousins had normal hearing and had never suffered from syncopal attacks The same applied to his four great grandparents and to the father s 11 brothers and sisters

The patient has since childhood suffered from fainting attacks lasting for about one minute The attacks were often associated with strenuous physical activity or oc curred when he became frightened or excited They were not accompanied by seizure or by passing of urine or faeces He had had attacks during his youth until the age of 17 At this age the attacks ceased and did not recur until he was 52 Then he suddenly fainted 10–12 times on the same day and was admitted to hospital

On admission he had auricular fibrillation that quickly changed to sinus rhythm with occasional ventricular ec topic beats After having fainted again he was transferred to the Intensive Care Unit for observation but suffered no further attacks there The ECG showed signs of an an teroseptal infarction and the enzymes were slightly raised He was discharged from hospital after 2 weeks and has suffered no further syncopal attacks since then

He is now being treated with propranolol 40 mg×3 *ECG shows a corrected Q T interval of 0 52 sec (0 54/55)* (Fig 1) and also an AV block I which may be caused by the β blockade therapy The blood electrolytes are nor

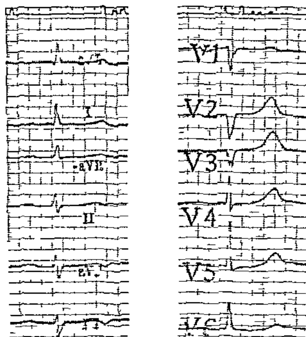


Fig 1 ECG from our patient (IV 8)

mal The audiogram shows an almost complete neurogenic hearing defect (Fig 2)

DESCRIPTION OF THE FAMILY

The Q T interval in the following text is shown as a corrected Q T interval according to the formula corrected Q T interval = Q $T/\sqrt{RR}$ (11) The upper limit is 0 The measured Q T and the heart rate are given in theses after the corrected Q T interval The fam bers I 1–2 II 1–4 and III 2 4–13 had no symp ing the syndrome but have not been examined III 4 and III 8 from whom we have ECGs The terval of III 4 is 0 46 sec (0 42/72) and of III 8 (0 38/75) (Fig 3)

III 1 The mother had had normal hearing suffered from fainting attacks She died of heart the age of 86 An ECG examination just before h revealed right bundle branch block with a Q T in 0 48 sec (0 42/75) No audiogram is available

III 3 The father had also had normal hearing no syncopal attacks during his lifetime An ECG taken just before his death showed right block with a Q T interval of 0 48 sec (0 38/95) gram is available

IV 1 A woman deaf mute since birth attacks *during childhood that continued into ad* She died in connection with a syncopal attack at 37 The post mortem revelaed no abnormalit form the *microscopic examination of the he* showed patchy fibrosis with slight infiltration An ECG recording taken just bef showed a Q T interval of 0 60 sec (0 60/60) or record of blood electrolytes are avilable

IV 2 A man with good hearing and not copal attacks ECG shows a Q T interval of (0 42/65) An audiogram shows the same neu ing defect as in IV 3

IV 3 A woman with good hearing (Fig 2) ar *to attacks Her ECG recording shows a Q T* 0 44 sec (0 42/70) An audiogram shows a r frequency hearing as in presbycusis

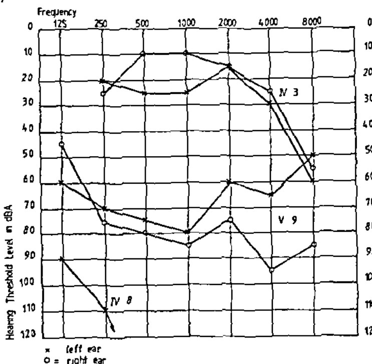


Fig 2 Audiograms of family m IV 3 IV 8 and V 9

Fig 3 Pedigree of the family Generations are indicated by Roman numerals and the members of the kindred may be identified from the generation number and sequence number The index case is no IV 8 Squares indicate males circles females □ ○ = normal ■ ● = QT syndrome ⊠ ⊘ = prolonged QT interval † = dead ↗ = propositus

A man deaf mute since birth who had had reg syncopal attacks He died at the age of 20 whilst ...g in an ice-cold mountain stream after haymaking ...ad fainted on his way out into the water ECG ...gram or blood electrolytes had never been recorded

A man with normal hearing and not prone to ...s He drowned at the age of 18 after falling through ...e ECG had never been taken

A woman with normal hearing not suffering from ...pal attacks ECG recordings show a Q-T interval of ...ec (0 42/70) Audiogram and blood electrolytes are ...al

7 A man deaf mute since birth who has suffered frequent syncopal attacks during adolescence ...e however ceased in early adult years ECG re...ngs show a Q T interval of 0 51 sec (0 54/55) The ...gram shows the same complete neurogenic hearing ...t as in IV 8 (Fig 2)

8 Our male patient described in the case report

9 A twin sister of IV 8 She had been deaf mute ...birth and had had syncopal attacks during child... The attacks ceased temporarily in the late teens but ...red at the age of 25 She drowned at the age of 27 ...it bathing alone No medical examination was ever ...

The eldest daughter of IV 6 She has been ...ined for attacks of palpitation which have been ...d in conjunction with a nervous heart Resting and ...cise ECG show a Q-T interval of 0 47 sec (0 36/100) ...audiogram is normal

The second daughter of IV 6 She has a hearing ...t and the audiogram shows a neurogenic defect of 60 dB (Fig 2) which however is not of the same type as that of the affected relatives According to otologists this defect is probably congenital She has not suffered any fainting attacks and both resting and exercise ECG show a Q-T interval of 0 40 sec (0 36/72) Even if the hearing defect is congenital it has probably no connection with the syndrome Hearing defect has not previously been described as the only expression of the syndrome

V 11 Daughter of IV 8 Always healthy with a normal audiogram ECG shows a Q-T interval of 0 45 sec (0 36/95)

The other members of generations V and VI are healthy and all have been examined with ECG and audiogram except VI 2 and VI 16 All recordings were within normal limits

DISCUSSION

Five members of the family have had the sur docardiac syndrome Three of them apparently died in connection with arrhytmic attacks It is known from previous studies that the syndrome has a high mortality rate (3) In about one third of all reported cases death has been caused by ventricu lar tachyarrhythmia or asystole It is important that the diagnosis is made as soon as possible as the arrhythmia can be treated successfully with ad renergic β receptor blocking agents (4 5 13)

A typical ECG shows a prolonged Q-T interval

and an unusually deformed T wave with varying amplitude the T wave may be positive, negative or biphasic A normal ECG does not eliminate the possibility of the syndrome because the Q T changes can be intermittent (3) If the syndrome is suspected repeated ECGs should be taken and possibly also an exercise ECG (12) It should be noted however that a prolonged Q T interval can be seen in connection with other conditions not related to the syndrome for example in myocardial necrosis or with certain stimulations of the au tonomic nervous system (6)

A prolonged Q T interval can also be seen in connection with ingestion of certain drugs such as quinidine in connection with hypokalemia or hypocalcemia in connection with cerebrovascular accidents or after Adams Stokes attacks (1 9) Q T changes related to the above conditions are however reversible The cause of the heart symptom in the Q T syndrome is still unclear In some cases primary damage to the myocardium has been suspected (7) Another theory is that an asymmetrical sympathetic stimulation of the myo cardium occurs (16) With a prolonged Q T interval the refractory period is considerably longer in cer tain parts of the myocardium than in other parts The difference in the length of the refractory period in different parts of the myocardium promotes the origin of ventricular fibrillation through the R on T phenomena (3)

The fact that the parents are cousins and that the syndrome occurs in only one generation strongly supports earlier observations that the surdocardiac syndrome has a recessive inheritance The moder ate prolongation of the Q T interval of unaffected members of the family (Fig 3) may as Fraser et al (2) postulated indicate that they are heterozygote carriers of the trait

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Carditis Associated with Mycoplasma Pneumoniae Infection

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RACT Among 560 patients with serologically med Mycoplasma pneumoniae infection, 25) had carditis (19 perimyocarditis, 6 pericardi luring the acute phase 9 patients required inten are After an average of 16 months follow up 11 nts with no previous signs of heart disease still ardiac symptoms or signs Thus carditis associ with M pneumoniae infection is a serious dis having cardiac sequelae more often than has to been supposed The pathogenesis of the car associated with M pneumoniae infection is sed including the possibility that in some cases evated titre in the complement fixation test is pecific A summary is given of the 33 cases ously presented in the literature

ords Mycoplasma pneumoniae pericarditis peri rditis

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art played by Mycoplasma pneumoniae in the gy of respiratory infections is generally 1 and has been widely studied Involvement of organ systems including the cardiovascular intestinal central nervous musculoskeletal rmal systems and the blood is less well ap ted Carditis has been considered a very rare lication of M pneumoniae infection only 33 have been presented so far in the literature 2 14 18–22 27 28 30 31 33–36 40 41 43) purpose of the present investigation was to ine the clinical picture and occurrence of the ovascular manifestations associated with M moniae infections

PATIENTS

asic series consisted of 560 patients treated during 77 in different hospitals in Helsinki who had had at a fourfold titre rise in the M pneumoniae comple fixation test (CFT) Information remitted with sera the main diagnoses was used to identify the pa with cardiac manifestations 69 patients were found is method

The hospital records of these patients were examined and those were selected who had carditis for which no causal agent other than M pneumoniae could be serologi cally and/or culturally suspected the number of such pa tients was 25 Another group selected were the patients whose titre rise had not been associated with a respiratory infection at the time or during the previous month and who had acute ischaemic heart disease or carditis for which besides the M pneumoniae infection an alternative cause could be suggested the number of such patients was 11

METHODS

Diagnostic criteria of carditis

The diagnosis of pericarditis was established if the patient had at least two of the following symptoms or findings Specific electrocardiographic (ECG) abnormalities con sisting of ST segment elevation without reciprocal de pression characteristic precordial chest pain pericardial friction rub or pericardial effusion The main criteria of perimyocarditis were ECG changes (transient ST T ab normalities arrhythmias and/or disturbances in conduc tion) for which no cause other than M pneumoniae infec tion was found In two patients the diagnosis was based solely on the changes in ECG neither of them had any previous history of cardiac disorder The others had in addition at least one of the following criteria transient cardiac murmur transient cardiac enlargement transient cardiac failure in a patient under the age of 25 for which no other cause was found or changes in echocardiography suggesting carditis

Serology

Every patient had at least a fourfold titre rise in the M pneumoniae CFT Sera from all but one patient were tested for complement fixing antibodies to herpes sim plex cytomegalo influenza A and B parainfluenza polio mumps respiratory syncytial measles and Coxsackie B 5 viruses ornithosis agent and toxoplasma no diagnostic rises were found Hepatitis B antigen was also negative in every patient but was not examined in one Most patients underwent even more comprehensive serological and bac teriological examinations

A micromodification of the CF technique was used The

Abbreviations CFT=complement fixation test ECG= electrocardiogram MI=myocardial infarction

and an unusually deformed T wave with varying amplitude the T wave may be positive negative or biphasic A normal ECG does not eliminate the possibility of the syndrome because the Q T changes can be intermittent (3) If the syndrome is suspected repeated ECGs should be taken and possibly also an exercise ECG (12) It should be noted however that a prolonged Q T interval can be seen in connection with other conditions not related to the syndrome for example in myocardial necrosis or with certain stimulations of the autonomic nervous system (6)

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The fact that the parents are cousins and that the syndrome occurs in only one generation strongly supports earlier observations that the surdocardiac syndrome has a recessive inheritance The moderate prolongation of the Q T interval of unaffected members of the family (Fig 3) may as Fraser et al (2) postulated indicate that they are heterozygote carriers of the trait

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ｌe III *ECG changes in 19 patients with perimy -ditis associated with M pneumoniae infection*

	N
changes only	5
changes +	
—degree AV block	3
degree AV block + ventricular	
topic beats	1
ial fibrillation	2
ial flutter with 2 1 and 4 1 conduction	1
ricular ectopic beats	1
dycardia + ventricular bigeminal	
topic beats	1
sodes of ventricular tachycardia	1
raventricular tachycardia	1
icular fibrillation	1
icular bigeminal ectopic beats	1
ent ventricular ectopic beats	1

Table V *Cardiac sequelae in 23 patients after a mean follow up time of 16 months*

	N	Age (y)
None	9	9 13 17 20 23 24 46 67 68
Cardiac failure for 1 y	1	1
Cardiac failure	3	57 62 66
Atrial fibrillation	3	26 30 59
Ventricular ectopic beats for 4 mo	1	39
Ventricular ectopic beats	2	29 59
1st degree AV block for 3 mo	1	20
1st degree AV block	2	32 44
Myocardial infarction 3 and 5 mo after perimyocarditis	1	25

had radiologically verified pneumonia In 8 its the onset of respiratory symptoms occur uring the week preceding the diagnosis of car in 6 within 1–2 and in 3 within 2–4 weeks The interval between the onset of respiratory toms and carditis was 11 days

e main non respiratory symptoms are listed in II Of the patients with pericarditis one was ctively free from cardiac symptoms and 5 had il chest pains and a temperature of over 37°C patient with pericarditis had palpitations and yspnoea. Of the patients with perimyocarditis no cardiac symptoms Sixteen patients had 9 chest pains 6 dyspnoea and 4 palpitations is of the 25 patients 7 had no cardiac symp- and 9 were in good condition despite symp-

IV *Manifestations of carditis*

	N
rditis	
hout pericardial effusion	2
h pericardial effusion	4
yocarditis	
ECG changes only	2
h ECG changes and cardiac largement	5
h ECG changes and transient rdiac murmur	8
h ECG changes transient murmur d cardiac enlargement	4
	25

toms Nine patients were so severely ill that they required intensive care Two patients required respirator treatment and one patient had temporarily a pacemaker because of bradycardia and ventricular ectopic beats One patient was successfully resuscitated from ventricular fibrillation

Findings

Transient murmur was found on auscultation in 18 patients in 12 this was friction rub Two patients had both friction rub and other kind of transient murmur

All patients with pericarditis had ST T changes in the ECG Two had transient atrial fibrillation in one of them this returned to sinus rhythm after an episode of nodal tachycardia. The ECG changes in the patients with perimyocarditis are presented in Table III Four patients had conduction disturbances 6 cardiac arrhythmias and 5 ventricular ectopic beats

Chest X ray showed that 4 patients with pericarditis had pericardial effusion in 2 the cardiac finding was radiologically normal In the perimyocarditis group 9 patients had transient cardiac enlargement The findings are listed in Table IV

Echocardiography was carried out in 4 patients In one patient the finding was normal one had pericardial effusion and 2 patients had a finding pointing to myocarditis

Laboratory findings

ESR was normal in 3 patients 10–50 mm/h in 11 and over 50 mm/h in 11 The leucocyte count was nor

Table VI *Eleven patients with cardiac disease of miscellaneous aetiology with at least fourfold rise in M pneumoniae CFT titres without simultaneous or preceding respiratory symptoms*

Pat no	Age (y)	Sex	Diagnosis	M pneumoniae CFT titre	Day of illness
1	1	♀	Hypovitaminosis B 1 perimyocarditis	<8 16	3 25
2	13	♀	Systemic lupus erythematosus pericarditis	16 128	NK NK
3	43	♂	Uraemia pericarditis	8 64	10 21
4	45	♀	Bacterial endocarditis (Staphylococcus albus)	8 64	10 22
5	47	♂	Bacterial endocarditis (α haemolytic streptococcus)	<8 32	NK NK
6	49	♂	MI	8 64	2 12
7	36	♂	MI	8 128	2 10
8	67	♂	MI	<8 32	15 26
9	63	♂	MI	8 128	5 15
10	52	♂	MI	8 32	1 10
11	47	♂	Arteriosclerotic heart disease cardiac failure	8 32	12 17

NK=not known

in 17 patients and 8 had leucocytosis of over 11 000/mm³ The blood values of alanine amino transferase and aspartate aminotransferase were determined in 22 patients Elevated levels were found in 12 more than half the cases usually both values were elevated Slightly elevated serum creatinine levels were found in 3 patients one of whom had acute transient glomerulonephritis with haematuria and proteinuria Antistreptolysin O titre determined in 23 patients rose temporarily to 560 in one patient

It has previously been suggested that in some cases of carditis raised titres in the CFT for M pneumoniae could be non specific and that low titres in the CFT point to this (39) The maximal M pneumoniae CFT titres of the patients with carditis were therefore compared with the titres of control patients with various manifestations of M pneumoniae infection The median of the maximal titres was higher in the carditis group than in the control group 74 24 and 57 87, respectively However the difference between the groups was not statistically significant ($p>0.05$) owing to the small patients with carditis

Antibiotic treatment

Eleven patients were given adequate treatment erythromycin, tetracycline or cline for at least a week The others recei biotics which are ineffective against M pne or no antibiotic treatment at all The mean of hospitalization in the groups with and adequate antibiotic treatment was 26 and respectively and the number of patients w manent cardiac sequelae 4 and 7 Thus with antibiotics known to be effective pneumoniae neither shortened the duratio ness nor clearly diminished the number of sequelae—a fact which may be of signi evaluation of the pathogenesis of carditis with M pneumoniae infection

Follow up and cardiac sequelae

The average hospital stay was 24 days All were invited to later check ups 2 did not

VII *Maximal M pneumoniae CFT titres in patients with carditis associated with M pneumoniae* *tion (A) carditis or acute ischaemic heart disease without respiratory symptoms and presumably of* *aetiology than M pneumoniae infection (B) and various manifestations of M pneumoniae infection*

	Maximal titres/N						Median titres
ɔ	16	32	64	128	256	512	
25)	3	3	6	8	2	3	74 24
11)	1	4	3	3	0	0	37 12
963)	62	198	274	166	160	103	57 87

remaining 23 were followed up as out patients n average of 16 months None of the patients during the follow up period

ily 2 of the patients in this study had had pre heart disease cardiac failure and myocardial ction respectively Both recovered from the itis regaining their previous condition In all ıg the check ups 9 patients were in good condi and without symptoms or signs of heart dis Fourteen presented with cardiac sequelae le V) in 3 patients symptoms disappeared dur he follow up Thus cardiac damage persisted a follow up period in 11 patients Three pa s—all of fairly advanced age, the youngest 57 old—developed cardiac failure Atrial fibrilla persisted in 3 patients ventricular ectopic ma s in 2 and first degree AV block in 2 A 25 year ıan with no previous history of cardiac disease loped myocardial infarction for the first time nths and for the second time 5 months after ıate ıyocarditis

ıne ace doubt has been raised before about the ssıb ible non specificity of M pneumoniae CFT in M ciation with heart complications (39) attention ee also focused on the patients who had acute rdı iac tissue damage without any preceding or si aneous respiratory infection that could explain rise at least fourfold in the M pneumoniae titre Eleven such patients were found (Ta VI)

Five of the 11 patients had carditis with at least a fold rise in the M pneumoniae CFT titre In the ology of these cases however there turned out some other alternative One patient had hypo- inosis B 1 one acute systemic lupus erythe osus and one exacerbation of uraemia Two ients had bacterial endocarditis one due to phylococcus albus and the other to Streptococcus group A Five patients who had myocardial infarction (MI) were screened for antibodies because carditis had been suspected in the early stages of the illness Lastly one patient developed acute cardiac failure as a consequence of arteriosclerotic heart disease

When comparing the maximal M pneumoniae CFT titres of these 11 patients with the titres of the 25 patients with carditis presented above one can see that the latter patients had higher titres (Table VII) (median 74 24 and 37 12) For these small groups the difference is not statistically significant However in the group of 11 patients the highest titre found was 128 while 5 (20%) of the 25 patients with carditis had titres higher than that

DISCUSSION

Carditis associated with M pneumoniae infection is commonly thought to be a rare disease only 33 cases have been published up to 1978 (Table VIII) Grayston et al (20) in 1965 were the first to present a case of heart complication associated with M pneumoniae infection a 20-year-old woman with transient pericarditis The first case report in which M pneumoniae infection was serologically reliably demonstrated was presented in 1969 by Lambert who described a 50-year old man with recurrent pericarditis (28) Since then 31 cases have been published of patients who had carditis associated with M pneumoniae infection (11 12 14 18 19 21 22 27 30 31 33-36 40 41 43) Of these 13 cases were presented as case reports The diagnosis of M pneumoniae was based in 2 cases on isolation and in 31 on CFT 26 of them having at least a four fold rise in titre

The age of 30 patients presented in the literature is known—only 5 of them were younger than 20—

Table VIII *Some aspects of carditis associated with M pneumoniae infection summary of [illegible] described in the literature*

Source	Age (y)	Sex	M pneumoniae test	Respiratory diagnosis	ECG changes	Diagnosis
Grayston et al (20)	20	♀	Isolation	NK	NK	Pericard[illegible]
Rosner et al (40)	18	♂	CFT 16–8	Pharyngitis	3rd degree AV block	Myocarditis
Hers (21)	NK	NK	CFT	NK	NK	Perimyocar[illegible]
Lambert (28)	50	♂	CFT 0–128	–	Flattened or inverted T waves in leads aVL V 4–7	Recurrent p[illegible] carditis
Gerzen et al (19)	NK	NK	Rising titre in CFT"	Pneumonia	NK	Myocarditis
	NK	NK	"Rising titre in CFT"	Pneumonia	NK	Myocarditis
Feizi et al (12)	30	♀	CFT 80–640	Pneumonia	Inverted T waves in leads III aVF and 1st degree AV block	Myocarditis
Fischer (14)	23	♀	CFT 30–480	Pneumonia	Inverted T waves in leads aVL V 2–6 and 1st degree AV block	Myocarditis
Lewes et al (30)	19	♀	CFT single convalescent titre≥256	Pneumonia	Inverted T waves in leads V 4–6	Myocarditis
	27	♀	CFT single convalescent titre≥256	Rhinitis	Flattened or inverted T waves in leads II, III aVF V 4–6 and coving of S-T segment in leads II III aVF	Myocarditis
Muller & Stelzner (35)	31	♀	CFT 40–160	Pneumonia	Inverted T waves in leads I II V 3–6 and depressed S-T segments in leads I II V 2–6	Myocarditis
Mårdh & Ursing (33)	15	♀	CFT 10–1 280	Pneumonia	Transient inverted T waves	Myocarditis
Naftalin et al (36)	71	♂	Isolation from blood and pericardial exudate after death	Pneumonia	Episodes of atrial flutter and bundle branch block	Perimyocar[illegible]
Khatib & Lerner (27)	20	♂	CFT single titre 128 (cold agglutinin titre 131072)	Pneumonia	Inverted T waves in leads II III aVF V 1–6	Perimyocar[illegible]
Mackay et al (31)	48	♂	CFT 32–128	Pharyngitis and pleuritis	Inverted T waves in leads I aVL depressed S-T segment in aVL and ventricular ectopic beats	Myocarditis
De Vos et al (11)	30	♂	CFT 4–64	Pneumonia	Inverted T waves in all leads	Myocarditis
Stuckey et al (43)	37	♀	CFT <8–512	Pneumonia	Inverted T waves and depressed S-T segments in leads II III aVF	Pericarditis
Holt et al (22)	34	♂	CFT 1 280–40	Pneumonia	Flattened T waves and S-T segment arching in leads II III aVF V 1–2	Myocarditis
Friedli et al (18)	1	♀	16–128	Upper respiratory tract infection	3rd degree AV block and right bundle branch block	Myocarditis
Maresh et al (34)	49	♀	CFT negative–64	Pneumonia	Q waves in leads I II III aVF and ST T changes in I aVR aVL V 1–6	Myocarditis
Sands et al (41)	54	♂	CFT>8–32	Pneumonia	Epicardial injury current	Perimyocar[illegible]
	44	♂	CFT 32–256	Pneumonia	Epicardial injury current	Pericarditis
	75	♂	CFT 8–64	Pneumonia	Epicardial injury current	Pericarditis
	60	♂	CFT 8–32	Pneumonia	Epicardial injury current	Pericarditis
	49	♂	CFT 16–1 024	Pneumonia	Non-specific ST T abnormality	Perimyocar[illegible]

VIII (Cont)

	Age (y)	Sex	M pneumoniae test	Respiratory diagnosis	ECG changes	Diagnosis
	54	♂	CFT 8–256	Pneumonia	Non specific ST T abnormality	Perimyocarditis
(41)	18	♂	CFT 8–32	–	Non specific ST T abnormality	Perimyocarditis
	52	♀	CFT <8–16	–	Non specific ST T abnormality	Pericarditis
	38	♂	CFT <8–16	–	Non specific ST T abnormality	Perimyocarditis
	27	♂	CFT <8–16	–	Epicardial injury current	Pericarditis
	30	♀	CFT <8–64	–	Epicardial injury current	Pericarditis
	35	♂	CFT <8–32	–	Epicardial injury current	Pericarditis
	65	♂	CFT 256–256	–	Non specific ST T abnormality	Pericarditis

not known

erage age being 37 The average age of the ent patients is almost identical 38 The patients arditis are therefore older than those in gen with M pneumoniae infection who usually are en the ages of 5 and 20 years The sex distri n of 30 of the previously presented patients is n 12 women and 18 men in the present study d 12 respectively

the 33 patients presented in the literature 25 respiratory infection in the recent case history ociated with carditis 19 had pneumonia and er respiratory tract infection in one with pleu for 2 patients no specific diagnosis was given patients had no history of respiratory infec In the present study the respiratory diagnoses ieir relative frequencies are quite comparable se presented previously

9 of the patients presented in the literature the finding is known 26 had ST T changes 2 of had first degree AV block and one ventricular ic beats One patient had third degree AV alone and one with right bundle branch One patient had episodes of atrial flutter with le branch block

e third or 11 of the patients presented pre ly had pericarditis the others perimyocarditis yocarditis The carditis was fatal in only one In this patient M pneumoniae was isolated at psy from a blood sample from the heart and the pericardial exudate (36) One patient was with a permanent third degree AV block (18) In eries of 13 patients of Sands et al (41) follow vas continued for an average of 47 months ng this period 2 patients died from causes not iected with the M pneumoniae carditis cardiac ptoms of unknown quality persisted in 3 and 8 had no cardiac symptoms by the end of the follow up period

It has previously been believed that carditis is a rare complication of serologically confirmed M pneumoniae infection Only sporadic cases had been published until Sands et al diagnosed 13 (9 2%) cases of carditis in a series of 141 patients with serologically verified M pneumoniae infec tion In the present series of 560 patients with sero logically confirmed M pneumoniae infection 25 (4 5%) had carditis This high frequency may partly be explained by the fact that the Helsinki University Central Hospital receives selectively the more diffi cult cases from the provinces the real frequency is lower

Carditis associated with M pneumoniae infection occurs in all seasons of the year as do M pneumo niae infections in general This complication was found every year of the study except in 1977 When the annual numbers of carditis cases were com pared with the numbers to be expected from the total number of M pneumoniae infections no sta tistically significant difference could be seen

Clinically carditis associated with M pneumo niae infection proved to be a serious illness 9 of the 25 patients required intensive care in the acute phase Five patients had dangerous frequent ven tricular ectopic beats one ventricular fibrillation and one episodes of ventricular tachycardia Two patients received respirator treatment In Sands se ries of 13 patients the results were fairly similar 6 patients were classified as mildly one moderately and 6 critically ill The cardiac sequelae in the pre sent study were more frequent however than has been previously described At the end of the follow up period of 16 months on average 10 of the 23

patients had cardiac damage none of them had had previous cardiac disease Moreover one patient a man of 25 had one episode of MI 3 months and another 5 months after recuperating from perimyo carditis

The pathogenesis of the carditis associated with M pneumoniae infection has not been elucidated In theory it is even conceivable that M pneumoniae has no part in the aetiology of these cardiac manifestations The following possibilities exist

A The heart disorder in question is caused by M pneumoniae directly or indirectly

1 By direct invasion of M pneumoniae into the heart This could occur through the lymphatic vessels connecting the throat and tonsils with the heart (1) via the circulatory system (36) or from the lower respiratory tract per continuitatem

2 By an autoimmune mechanism M pneumoniae infection may cause such a change in some component of the heart tissue that an autoimmune response is produced and this causes damage to cardiac tissue On the other hand it is possible that *the antibody is produced primarily against the M* pneumoniae antigen but owing to common characteristics of some component of cardiac tissue and M pneumoniae lipid antigen a cross reaction is produced against the cardiac tissue In 1943 Thomas et al (44) showed that the cardiac tissue of beef had an antigen which reacted positively with convalescent sera from patients with primary atypical pneumonia which is nowadays known to be most commonly caused by M pneumoniae so this may have antigen characteristics in common with heart tissue

A similar autoimmune mechanism has been considered as one pathogenetic possibility in cases of pancreatitis in which M pneumoniae CFT titres have been elevated (29) Biberfeld (3) showed that brain tissue and M pneumoniae lipid antigen have traits in common so autoimmune phenomena may play a part also in the pathogenesis of central nervous system complications of M pneumoniae infection

Brunner et al (5 6) and Fernald et al (13) have suggested that the pneumonia due to M pneumoniae may be an immunopathological disease its severity depending on earlier sensitization by one or *more silent infections It is also possible that the* non respiratory manifestations of serologically confirmed M pneumoniae infection such as carditis arthritis and central nervous system infections are caused by an immunological mechanism pathogenesis of these could be similar to th lated for rheumatic fever In this conne interesting to note that M pneumoniae an tococcus group A have antigenic prope common Brunner et al (6) have shown th immunoprecipitating antibodies to M pne were blocked by lipids from selected s Streptococcus group A and Staphylococcu

3 An increased tendency for blood co and intravascular thrombosis has been not sociation with M pneumoniae infections (37 38 42) Possibly some part of the heart tations associated with M pneumoniae i can be explained on the basis of microth the coronary arteries It is interesting th study 5 MI patients who had elevated M niae titres although no respiratory manif were suspected in the early phases of the having carditis

B Alternatively the carditis is not n due to M pneumoniae infection the rise *M pneumoniae can be non specific or* t can have a double infection

1 Mycoplasma other than M pneumo be the cause of the infection and there body cross reaction and a false positive r even though so far no mycoplasma spe than M pneumoniae is known to be a hum gen

2 Another agent such as a virus or an primarily cause damage to cardiac tissue change some component of the heart tiss a way that an autoimmune reaction is Since cardiac tissue may have antigen pr common with the M pneumoniae lipid an M pneumoniae CFT then gives a false result

3 A further possibility is a double subclinical or respiratory M pneumoniae and simultaneous carditis caused by anoth gen

In this series of 25 carditis cases the sim seasonal and annual distribution and the a imately equally high maximal titres in CF other M pneumoniae infections point to a aetiological role for M pneumoniae This *sion is supported by the case described by* et al (36) in which M pneumoniae was iso autopsy from the pericardial exudate and blo

The carditis associated with M pneumo

is not necessarily always due to one and the mechanism More than one of the possibilities ted above may play a role in the pathogene is view is supported by the observation that ie patients carditis more or less coincided ne respiratory symptoms while in others it ed more than 2 weeks after they commenced me cases no respiratory symptoms were ed in these infection may have been sub l

it significance should then be attributed to the the M pneumoniae titres of the 11 patients ieart disease presumably caused by some other than M pneumoniae and who did not t with any signs of a respiratory infection? It ible that these patients did have a subclinical eumoniae infection Another possibility is hen cardiac tissue is damaged in some way oimmune response is produced leading to a eaction and a false positive result in M pneu e CFT as described above Non specificity elevated titres is supported by the observa hat the maximal M pneumoniae titres were in this group of 11 patients than in the group patients with carditis The 5 MI cases among 11 patients are those in whom M pneumoniae 1 theory have played a causal role since a icy to blood coagulation and intravascular posis has been observed in M pneumoniae ons

tions due to M pneumoniae are not un on accounting for 7–27% of all cases of pneu (4 16 17 20 24 25 39) In addition more on than pneumonia are the other types of atory involvement caused by M pneumoniae 9 15) Since according to this investigation as may be a complication in as many as 4 5% ologically confirmed M pneumoniae infec it is reasonable to examine the ECGs of pa treated in hospital for respiratory infections M pneumoniae aetiology is present or sus d Further the M pneumoniae CFT can be mmended as a routine method for examining its with carditis of unknown aetiology

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A Controlled Study of Early Discharge after Uncomplicated Myocardial Infarction

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RACT Out of 383 myocardial infarction (MI) its aged below 70 years 252 (66 %) were judged the third day in hospital to have had uncompli infarctions These patients were allocated at m to two groups one of which was given treat for 8 days and the other for 15 days No sig nt differences in mortality, morbidity or in ity for work could be detected during the month period of follow up The findings thus rt previous conclusions that early discharge hospital after uncomplicated MI is not as ed with greater risk for the patient than later arge

words myocardial infarction early discharge zation

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ment of acute moycardial infarction (MI) was haracterized by prolonged immobilization of atient and long periods of hospitalization Dur he 1950 s however it was shown that the d of bed rest could be substantially shortened iospital treatment reduced to 3–4 weeks (3 12

iring the last decade the period of hospital ment has been further cut down to about two s for patients with uncomplicated MI without increase in mortality (1 8 11 22 24) Several stigations indicate that the period of hospital ment can be further reduced (2 5 7 16 17 23 out there are few controlled studies (9)

ie aim of this prospective randomized con ed investigation was to study whether patients uncomplicated MI could be discharged from ital after eight days treatment instead of 15 out any increase in mortality morbidity or in icity for work

PATIENTS AND METHODS

The study was performed at Falu Hospital which has a catchment area comprising industrial towns small towns and villages and rural areas with a population of 128 000 The study comprised patients treated at the Coronary Care Unit (CCU) for acute myocardial infarction with onset less than 48 hours before admission to hospital Patients who had sustained MI during the preceding three months or who were above 70 years of age were excluded The diagnosis of MI was based on conventional criteria (27) The patients were kept under observation in the CCU for three days after which the survivors were as sessed by one of the physicians participating in the study Patients with any of the following contraindications after 72 hours in hospital were excluded 1) Maximal serum aspartic aminotransferase (S ASAT) ≥5 5 μkat/l (S-GOT ≥300 IU) 2) Persistent arrhythmias despite treatment second degree and complete AV block multifocal ventricular extrasystoles supraventricular tachycardia ≥110/min 3) Chest pain requiring continuous treatment with analgesics 4) Heart failure in spite of treatment 5) Cardiogenic shock 6) Pericarditis with a temperature of ≥38 5 The remaining patients were randomly allocated to two groups with different mobilization programmes

After 72 hours the patients were transferred to a second ary CCU where they were monitored on an oscilloscope for a further four days One group of patients were allowed to sit up for periods of altogether 1½ and 3 hours respectively on the fourth and fifth days of treatment They were given their clothes and allowed to move about the ward from the sixth day and were discharged after the eighth day of treatment (the 8-day group) The patients in the other group were mobilized gradually after the third day and allowed to get out of bed from the 12 day and discharged 15 days after admission (the 15-day group) The patients in either group who were unable to follow the mobilization programme were excluded from the study In addition the patients were assessed with respect to the contraindications listed above and any new complicating disease (bronchial pneumonia thrombosis embolism) on

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Abbreviations MI = myocardial infarction CCU = coro nary care unit S ASAT = serum aspartic aminotrans ferase

Table I *Main reasons for exclusion of patients from the study after the third day of treatment in each group*

	8-day group (n=21)	15-day group (n=24)
Angina pectoris	9	7
Arrhythmia	2	5
Heart failure	2	3
Thrombosis	1	1
Postmyocardial infarction syndrome/bronchial pneumonia	2	1
Tiredness/inability to cooperate	5	7

Table III *Number of reinfarctions and c missions to hospital during the 3 month fol each group*

	8-day group	15-da
Fatal reinfarction	5	2
Non-fatal reinfarction	6	3
Other hospital treatment	4	9
Angina pectoris/suspected infarction*	2	1
Arrhythmia	1	1
Cardiac decompensation	1	[illegible]

* Chest pain and unspecific S-T or T wave abn and normal transaminases or characteristic enzym tion within the normal range

the eighth day and were excluded when appropriate At discharge all patients were given the same rehabilitation advice and smokers were advised to give up smoking

During the three month follow-up the patients were controlled at the department s outpatient clinic one week after discharge and six and 12 weeks after onset of infarction All deaths reinfarctions and periods of hospital treatment due to cardiac causes were also recorded

RESULTS

ring the period Sept 1 1975–Jan 31 1978 383 tients were treated for MI at the CCU Forty eight patients died and 83 were excluded owing to contraindications during the three days 57 patients had max S-ASAT≥5 5 μkat/l 34 persistent arrhythmias 14 severe chest pain 11 heart failure with or without cardiogenic shock and 3 pericarditis

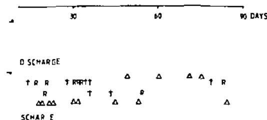
Table II *Sex age number of smokers occurrence of previous diseases cardiac volume and maximal S ASAT during hospital treatment of the patients in each group*

	8-day group (n=106)	15-day group (n=100)
Women (%)	24	18
Mean age (y)	60 7	61 9
Smokers (%)	42	50
Previous diseases (%)		
MI	16	22
Diabetes mellitus	13	4
Hypertension	24	29
Cardiac volume (ml/m²)	504	511
S-ASAT (μkat/l)	1 9	2 0

with a high temperature Of the remaining tients 21% of whom were women 128 were cated to the 8-day group and 124 to the group Forty five patients were excluded the study after the third day (Table I were no statistically significant differenc tween the groups in this respect In the group one 61 year-old man died from tion and cardiogenic shock with papillary rupture almost four days after admission 24 patients in the 15-day group who cluded owing to complications 20 (83% withdrawn during the first eight days other two during the ninth day Altoget patients were excluded from the study complications and 13 (10 2%) of them died hospital Only one (0 5%) of the 207 patients to have uncomplicated MI died Twenty-n 57 patients with S-ASAT max ≥5.5 μkat/l fulfil any of the other criteria for exclusion excluded solely because of the transamin Of these 29 patients four (14%) died and fered reinfarction during follow up

Thus 106 patients were discharged after days and 100 patients after 15 days Det age previous diseases and certain variables hospital treatment for these two groups are Table II At the time of discharge there statistically significant difference between groups with respect to treatment with diuretics antiarrhythmics or β blocking age

During the period of follow-up five pa (4 7%) died due to reinfarction in the 8-day and two (2%) in the 15-day group (Table III)



Deaths (†) non fatal reinfarctions (*R*) duration of
ıl treatment (▨) and other periods of hospital treat
uring the follow up period (Δ)

ven patients who died had been readmitted ed in hospital after several days One patient 8 day group suffered reinfarction six days lischarge and died shortly after readmission rection showed a very extensive original in on There were also six and three non fatal rctions in the 8 day and 15 day group respec The difference is not statistically significant patients in the 8-day group and nine in the group were readmitted for other cardiac ns Fig 1 shows when the reinfarctions and periods of hospital treatment occurred during llow up period

he 252 individuals allocated to the two groups days after admission 91 (71%) in the 8 day and 86 (69%) in the 15-day group had thus not r required additional hospital treatment three s after onset of infarction

he follow up three months after onset of in n 48% of the patients in the 8-day group and n the 15 day group reported symptoms of pectoris Twenty per cent and 23% respec suffered from dyspnoea on exertion and 2% h group had clinical decompensation

the 206 patients discharged alive 54% in the group and 47% in the 15-day group were ng at the time of onset of infarction Within months 65% and 49% respectively were o resume work in the same or a lighter occupa

the patients with uncomplicated infarction 18) had diabetes mellitus compared to 23 (18%) patients excluded because of complications teen of the 18 diabetics belonged to the 8-day and one of these 14 patients died and two red non fatal reinfarctions during the follow up d One of the four diabetics in the 15 day group red reinfarction later

DISCUSSION

There is still some uncertainty as to the optimal length of hospital treatment and immobilization in so-called uncomplicated MI It has been suggested that rapid mobilization might interfere with consolidation of the infarcted myocardium and increase the size of the infarct thereby increasing the risk of rupture of the ventricle (15) and development of ventricular aneurysm (19 20) Furthermore arterial hypoxia in the acute phase of infarction might also increase the risk of reinfarction and arrhythmia Several studies during the last decade have contradicted this hypothesis however (8 11 25) A longer period of hospital treatment might enable malignant arrhythmias to be detected and treated *thus reducing sudden deaths These conditions* usually occur early in the course of infarction however and the occurrence of life threatening complications that are amenable to treatment is low after the first week of treatment (7)

More rapid mobilization might reduce the risk of thrombosis embolism and pulmonary complications Many authors have pointed out the psychological advantages of both a short period of immobilization and a short stay in hospital (14 24) This may lead to more rapid rehabilitation and possibly a more rapid return to work A shorter period of hospitalization also reduces the demand for hospital beds and this probably entails major economic gains (16)

At present there are no reliable criteria for predicting after 2–3 days treatment whether or not an infarction will have an uncomplicated course Different laboratory variables during the first days have been used to identify patients with extensive myocardial damage and/or a high risk of arrhythmia Several indices for judging the long term prognosis after MI have been constructed (10 21 26) These indices have been fairly reliable for predicting cardiovascular death but not non fatal reinfarction

Sinus tachycardia during the first day of treatment persistent S T segment elevation certain ventricular arrhythmias second degree and complete AV block and chest pain during the first week in hospital have been used as prognostic variables in several studies concerning early discharge (2 5 27) In other studies patients with persistent cardiac decompensation (7 9 11 18) hypotension (16 17 24) atrial tachycardia (17 22) or cardiac enlarge

ment (6 22) have been considered to run an increased risk of complications

Similar exclusion criteria were applied in this study Like Wilson and Pantridge (28) we excluded patients with high concentrations of S ASAT as the degree of enzyme elevation is considered to constitute a measure of myocardial damage (4 13) We also considered it unlikely that patients with pericarditis pain an a high temperature during the third day of treatment would be able to follow the mobilization programme and these patients were therefore also excluded Of the 14 patients who died in hospital after the third day of treatment 13 (93 %) had been excluded from the study so that our criteria identified patients at risk with a rather high degree of accuracy

After three days of treatment three quarters of the patients were considered to have an uncomplicated infarction Additional patients were excluded during the following days however mainly because of angina pectoris and tiredness Thus 62% could be discharged in accordance with the original plans In previous studies with 7–9 days hospital treatment the corresponding proportion of uncomplicated infarctions has varied between 49 and 76% (5 7, 9) One patient in the 8 day group died on the fourth day and it is difficult to judge whether or not this death could have been prevented by a longer eriod of bed rest

The distribution by age and sex and the incidence f so called risk factors for MI—number of previous infarctions, hypertension and smoking—did not differ between the 8 day and 15-day groups Diabetics were overrepresented in the 8-day group however There was no difference with respect to treatment with digitalis diuretics or other antiarrhythmic drugs between the two groups at the time of discharge or during follow up

Altogether seven patients (3 4%) died during the first three months all from reinfarction which is in fairly good agreement with mortality figures in other studies (2, 9) The patient in the 8 day group who died six days after discharge might have been saved if he had been kept in hospital Of the 22 patients (10 7%) who were readmitted to hospital and survived 10 belonged to the 8 day and 12 to the 15 day group Six and three of these patients respectively, had verified reinfarctions whereas the remainder were mainly given the diagnosis of suspected infarction/angina pectoris The shorter period of hospital treatment thus did not increase the number of readmissions during follow u statistically significant difference was found number of subjective cardiac symptoms s angina pectoris and dyspnoea This find further supported by the fact that about th number of individuals in both groups who ha working at the time of onset of infarction we to return to work within three months in agr with the report of Tucker et al (25)

Diabetic patients who sustain MI have be sidered to need longer periods in hospital o the poorer long term prognosis (7) This te was also found in our study The number of ics is too small however to permit an ana whether or not a longer period of hospital tr would improve the prognosis for these pati

To summarize we have not been able to significant differences in mortality, morbidi capacity for work in patients with uncom MI who were discharged after 8 days com those kept in hospital for 15 days Patients not had MI during the preceding three m who were more than 70 years of age or defined complications during their stay in were excluded from the study With the criteria applied a low risk group among th tion patients could be identified Wheth diabetics should be judged otherwise in th is uncertain

We have started mobilizing the patients third day but this can probably be done e 14, 24) During the final part of the stay i great attention should be paid to the pati jective condition and symptoms such as tir an abnormal reaction to light physical ex total period of eight or nine days hospital t would seem to be appropriate in most cas complicated myocardial infarction The p hospital should be individualized however patient s domestic situation should be ta consideration, so that early discharge is step in a successful rehabilitation and se preventive programme

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Comparison of Streptokinase with Heparin Late Results in the Treatment of Deep Venous Thrombosis

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RACT Nineteen cases were reinvestigated 8–
rs after treatment with SK or heparin Judging personal interviews foot volumometry and ography, treatment with SK appears to be more able since it was less often followed by late postthrombotic changes

ords streptokinase heparin venous thrombosis
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treatment of acute deep venous thrombosis) streptokinase (SK) is used in order to dis the thrombus and preserve the valves of the is system and thereby to prevent the de ment of the postthrombotic syndrome (4 11)

is still debatable whether SK is a more ef ous drug than heparin Only four prospective mized comparative investigations of the two ies in altogether 117 patients are on record 5 18 23) Judging from the phlebograms the ibus promptly disappeared in only 3 (5%) of 7 patients given heparin compared with 21) of those 60 given SK

s however known that several years may before appearance of sequelae (2) Documen of the long term beneficial effect of SK there equires a long follow up but only few really eviews of such patients are available (8 14) holds also for studies of SK versus other drugs 9 15 23)

tween 1963 and 1969 Robertson et al (17 18 eated 57 patients (3 treated on 2 occasions) in prospective randomized series The purpose present investigation was to re-examine these nts with regard to postthrombotic sequelae SK or heparin treatment

STUDY POPULATION

Robertson s three coded series of altogether 57 patients with acute DVT had been treated with SK or heparin All the patients had had symptoms for at most 96 hours before treatment The doses and duration of treatment are given in Table I

In *series I* (20 treatments 19 cases) the diagnosis had not been verified phlebographically in the first 9 patients who were therefore not included in the present series Of the remaining 11 cases one was excluded because he had had thrombosis of a subclavian vein One patient had been treated twice on the first occasion with heparin and on the second with SK He had died several years after the treatments Another 2 patients treated with heparin and one treated with SK had also died Thus 5 patients were left for the present investigation 2 treated with heparin and 3 with SK

In *series II* (16 treatments 16 cases) 6 of the 8 patients treated with heparin and 2 SK treated patients had died Two could not take part because of advanced age and associated difficulties One patient treated with SK had developed severe arterial insufficiency in both legs and had to be omitted This left 5 patients for the present study 2 treated with heparin and 3 with SK

In *series III* (16 treatments 14 cases) one patient had *been treated twice for DVT in the same leg first with* heparin and due to recurrence 2 weeks later with SK One patient was not included because his DVT was confined to the calf veins only Three of the heparin treated and two of the SK treated patients had died One patient had emi grated and one could not be traced Two cases treated with heparin and 4 with SK plus the patient first treated with heparin and later with SK were thus available for the present study

In the *supplementary series* in which 8 patients had been given SK 4 had died and one had emigrated This left 3 patients for reinvestigation

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Abbreviations DVT=deep venous thrombosis SK= streptokinase EV=volume expelled EV_{rel}=EV relative to foot volume $\dot{Q}$=rapid phase of refilling flow after exercise flow relative to foot volume $\dot{Q}/EV_{rel}$=time factor t i d =titrated initial dose

Table I *Administration of SK number of treatments with SK or heparin and number of reinvestig*

	Series I (treated in 1963–65)	Series II (treated in 1965–67)	Series III (treated in 1967–68)	Supplementar (treated in 196
Initial dose	1×t i d for 30 min+ 1×t i d for 60 min	2×t i d for 90 min	2×t i d for 90 min	500 000 IU of S for 60 min
Maintenance dose of SK (IU/h)	*50 000*	*100 000*	*100 000*	*100 000*
Total duration of treatment (h)	12	24	72	72
No of treatments				
SK	12	8	8	8
Heparin	18	8	8	8
No of reinvestigations (1977)				
SK	3	3	5	3
Heparin	2	2	2	3

As for the causes of death in the above mentioned patients venous thrombosis had been noted in one as a contributory cause However he died several years after treatment in the coded series

Summing up 13 patients treated with SK and 6 treated with heparin took part in the late review

METHODS

The re-examination included personal interview physical examination foot volumometry and phlebograhy

Interviews The patients were questioned concerning the duration of their illness caused by DVT as well as any complications and operations

Physical examination included careful inspection for ose veins hypostatic eczema ulcerations and difference between the circumferences of the calves The patients were classified according to the following criteria 0) No change 1) Moderate changes with oedema varicose veins hypostatic eczema and a difference of up to 1 5 cm between the greatest circumferences of the calves 2) "Severe or more pronounced changes than in the moderate cases ulcerations and a more marked difference between the greatest circumferences of the calves

The function of the venous system was assessed from changes in the volume of the foot—*foot volumometry*—with an apparatus *designed by Thulesius* et al (22) and tried out clinically by Norgren (12) The parameters used are EV=volume expelled (ml) as calculated from the reduction of foot volume during exercise EV_{rel}=volume expelled relative to foot volume (ml/100 ml) $\dot{Q}$=rapid phase of refilling flow after exercise flow relative to foot volume (ml/100 ml×min) $\dot{Q}/EV_{rel}$= time factor (min^{-1})

The control series consisted of 30 observations in 15 persons aged 14–42 years and a sample (14 observations) of 7 older individuals aged 58–72 years—Norgren (12) having shown that the reduction in volume is significantly smaller in elderly persons while restitution of the flow is the same in both groups The mean values and S D of the volumometric findings in the control groups are given in Table II

Phlebography was performed according to a standardized technique (13) The phl amined for postthrombotic changes of the dee veins Postthrombotic changes and incompe ileofemoral veins are betrayed by retrograde flow trast medium during the act of straining and regularities of the veins and absence of valves

Physical examinations and volumometric s foot were carried out in 1977 If phlebograph follow up had shown postthrombotic changes struction of the valves and collateral vessels graphy was not included in the review

RESULTS

Series I (Table III)

This series consisted of 5 patients 3 of wh been treated with SK and 2 with heparin dosage of SK (50 000 IU/h for 12 h) was the phlebograms obtained after treatment show any signs of thrombolysis In none was the affected leg completely asympto the review in 1977 No difference in subjec objective parameters could be tween the SK and heparin treated patients

Table II *Volumometric parameters in the groups (mean ±1 S D)*

	Control groups	
	Aged 16–42 (*n*=30)	(*n*=14)
EV (ml)	14 9±4 6	11 7±1
EV_{rel} (ml/100 ml)	1 4±0 4	1 1±0
$\dot{Q}$ (ml/100 ml×min)	2.5±1 0	2 6±1
$\dot{Q}/EV_{rel}$ (min^{-1})	2 0±1 3	2.5±1

n II (Table III)

series 6 patients remained but one had de d severe arterial insufficiency in the legs and) be omitted Of the 5 patients available for estigation 3 had been treated with SK and 2 heparin A high dose of SK (100 000 IU/h as nance dose) had been given for a relatively time (24 hours) In only one patient (no 4) did ography show thrombolysis after treatment in proximal part of the calf veins and popliteal No postthrombotic changes were seen at the ography in 1977 This was the only patient had no symptoms at the time of the review t 8 who had had thrombosis of both legs on occasions and had been treated each time with n showed hardly any postthrombotic es clinically or phlebographically at the re In patient 16—who also had had DVT in both n two occasions and who had not been l for the first episode in one limb but had ed SK on the second occasion—the post rotic changes were the same in both limbs

III (Table III)

ses remained (8 treatments) plus 3 from the *mentary series* in which all patients were K The period of treatment was 72 hours Of ments with SK 6 showed thrombolysis l and 2 (the same patient with DVT on two ons in different legs) showed significantly ysis of the thrombus in the limb treated with n in the other treated with heparin Cases 10 (also the same patient first treated with and within 2 weeks with SK for progress of VT in the same leg) showed after the SK ent only a slight thrombolysis of no clinical ance Patient 15 treated on one occasion eparin because of DVT of one leg and later K because of a similar affection of the other d no further change after the SK treatment t 22 who also served as his own control had ided significantly better to SK

follow up examinations thus showed an im nent of the veins after SK as well as heparin ent The patients with initial thrombolysis d clinical changes of moderate and se type less commonly than those who had not ny thrombolysis Table IV summarizes the of the treatments in the different series on the clinical status at the reinvestigation

The patients with thrombolysis had no or insig nificant postthrombotic symptoms while those who had had no lysis showed postthrombotic changes

DISCUSSION

SK has been used as a thrombolytic agent for more than 15 years yet there is still much controversy about the value of such treatment Many authors have reported complete lysis in a high percentage of these cases (6 8 9 15) However treatment with SK is expensive and more often attended by side effects than treatment with heparin Since sev eral years may pass before the postthrombotic syndrome appears (21) proper evaluation of any advantage of SK must be based on reviews carried out long after termination of the initial treatment But such reviews are few and some of them have been done rather early after treatment (Kakkar et al (9) 6–12 months Olow et al (14) 1–10 months (no control group) Porter et al (15) 3–12 months Bieger et al (3) 3–4 months Johansson et al (8) 6–50 months (no control group))

In the present study the coded series were re viewed 8–14 years after treatment The number of patients examined was fairly small—only 19 In series I and II altogether 10 patients the dose of SK given was smaller than that conventionally re commended Thus the patients in series I were given a maintenance dose of 50 000 IU/h for 12 hours and the patients in series II 100 000 IU/h for 24 hours No thrombolysis was demonstrable on phlebographies taken immediately after the treat ments nor were there less postthrombotic symp- toms in the SK group at the late follow up in vestigation SK treatment that lasts for only 12 or 24 hours is obviously not long enough In a phlebographic study Olow et al (14) found that complete thrombolysis required treatment for 72–96 hours Such lengthy treatment (100 000 IU/h for 72 hours) was given to the patients in our series III and the supplementary series It was obvious that thrombolysis could be achieved with this regimen The initial standard dose in the supplementary group (500 000 IU) seems to be adequate since only one of the patients in the three coded series treated by Roberton (16) had a t i d of SK of more than 250 000 IU These findings are in accordance with those of Olow et al (14) and Schmutzler (20) Of special interest in series III an e s

Table III *Rein est gated pat ents tl e effect of ı tıal treat nent c nd co ıd tı ıs at revıe ın I*
R rıght L left P patholog cal N normal

Case no	Treat ment	Affect ed l mb	Phlebo gram after treatment	On sıck leave	Follow up ın 1977 Clın cal symptoms	EV$_{re}$ (ml/ 100 ml)	$\dot{Q}$ (ml/ 100 ml ×mın)	Q/EV$_{re}$ (m n)	Phlebog
Ser es I									
11	1963 SK	R	St quo	Earl er ret red at 60 y (asthma)	R 1 L 1	P P	N P	P P	1964 st
12	1963 SK	R	St quo	4 mo	R 1 L 2	Not performed (gonarthros s)			1965 st 1977 st
14	1964 Heparın	R	St quo	2 weeks	R 1 L 1	Refused ınvest gat ons			
17	1965 SK	L	St quo	2 y	L 1 R 1	P P	P P	P P	1969 st 1970 st
20	1965 Heparın	L	St quo	4–6 weeks	L 1 R 1	P N	P P	P P	1966 st
Ser es II									
2	1965 SK	L	St quo	2 weeks	L 1	N	P	P	St pos
4	1966 Heparın	L	Lys s	Ret red	L 0	Not performed (Cox arthrosıs)			Norma
8	1966 Heparın	R	St quo	1 week	R 1 L 1	N N	P P	P P	Norma Deep
14	1966 SK	R	St quo	7–8 mo	R 2	P	P	P	1967 a st pc
15	1966	R	?	1 mo		Not performed			
16	1967 SK	L	St quo	2 3 mo	L 1 R 1	N P	P N	P P	Refuse
Ser es III and s pplementary ser es									
1	1967 Heparın	L	Lys s	4–6 weeks	0	P	N	P	Refuse
2	1967 SK	R	Lys s	4–6 weeks	0	P	P	P	Refuse
4	1967 Heparın	L	St quo	6 mo	2	P	N	P	St po
7	1968 SK	R	Lys s	2 3 weeks	(1)	P	N	P	Refuse
10	1968 Heparın	L	St quo						
11	1968 SK	L	Lys s 5 cm	4 weeks	(1)	P	P	P	Refuse
14	1968 SK	L	Lysıs 32 2 cm (progr 4 d after SK ınf)	Retıred	0	Not performed (sen l tas)			1971 st but ın
15	1968 SK	R	St quo (progr 4 d after SK ınf)	1 y	R 1 L 1	N N	P P	P P	1971 st
17	1968 SK	R	Lysıs 23 5 cm	2 3 weeks	(1)	N	P	P	1971 no s gns
21	1969 SK	L	Lysıs 20 cm	2 3 weeks	0	P	P	P	1971 st but n
22	1969 SK	R	Lys s 20 cm		R 0 L (1)	N P	N P	N P	1971 st but n

* Crıterıa 0–2 see Methods

3 left leg heparin treatment

g leg 6 weeks after treatment
T left leg heparin treatment

right leg heparin treatment 1969–71 operated on
both legs because of st post thromb
arlier DVT left leg treated with thrombectomy
ectomy 1973 DVT right leg heparin treatment

975 DVT left leg
reatment both times

occlusions right leg amputated 1977 ulcus
leg skin transpl 1972–73
right leg clinically
ent

Re distally of popliteal veins bilat

Re

St pos

Refuse

f the thrombus within 2 weeks
treatment

Re

T left leg heparin treatment
post thromb

T left leg heparin treatment
post thromb

Table IV *Comparison between the different types of treatments initial effects and clinical condition at the late investigation*

Clinical status	Initial effect	Type of treatment Hepa rin	SK 12 h	SK 24 h	SK 72 h
0	6 lysis 0 st quo	2			4
(1)	3 lysis 0 st quo				3
1 or 2	0 lysis 11 st quo	4	3	3	1

* Criteria 0–2 defined in Methods

plementary series are 3 patients (nos 1 2 (the same patient) 15 and 22) who were treated with SK on one occasion for DVT in one leg and with heparin on another occasion for DVT in the other leg Two of them (the first and the last case) showed a significantly better response to SK than to heparin the third showed no difference

When partial or complete thrombolysis is achieved in the femoral vein and proximal thereto most phlebologists agree that no severe post thrombotic symptoms e g ulcerations need be feared even if postthrombotic sequelae occur in the popliteal and calf veins (1 7) Our patients in whom the femoral thrombus had been lysed but who displayed remnants in the distal veins pre sented only fairly mild or no changes with slight oedema and/or small varicose veins This is in agreement with the follow up investigations by Widmer et al (24) who found that none of their patients who demonstrated a partial thrombolysis developed crural ulcus

Summing up severe postthrombotic symptoms seemed to be less common in the group treated with SK for 72 hours and the complications of the thrombosis were more severe in patients treated with heparin or SK for only 12 or 24 hours (Table IV)

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Blood Pressure in 60-Year-Old Men

Findings in a Health Survey and Some Comparisons with 50 Year Old Men in the Same Community

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RACT A population survey of 60 year-old (n=331) was performed in Uppsala The preva of hypertension defined as established hyper and those having an unknown diastolic blood re (DBP) of ≥105 mmHg was 19.3% Of the ensive population 35 9% had not been de previously In the treated group 43 9% were controlled regarding the BP level Thus 64 1% total hypertensive population at the age of 60 were either undetected or inadequately con

Excretion of urinary electrolytes was also ted in this work All participants of the health except four performed a 24-hour collection of following the health examination Care was with endogenous creatinine clearance Negative gnificant correlations were noted between ex of sodium and potassium in urine and DBP in the group (n=23) of untreated hyperten In a population sample (n=135) of healthy ts devoid of medical treatment in the same ation survey, a positive and significant correla as noted between the systolic BP and the uri excretion of sodium Thus up to a certain BP there is a pressure diuresis and at higher BP the kidney retains electrolytes

ords essential hypertension urinary electrolytes al intake hypertension

Med Scand 206 99 1979

ated blood pressure (BP) has been found in epidemiological studies to be a major risk r for cardiovascular and cerebrovascular dis Thus it is an important task to find the rtensive population and to commence treat In an attempt to reduce the high cardiovascu morbidity and mortality in middle aged men rtension should naturally be treated before the al age is reached

the present study a 60-year-old male popula tion was screened The purpose was to compare the 60-year-old hypertensive men with a 10 years younger group of men in the same community (13) as well as to perform some special studies on the excretion of urinary electrolytes This survey was thus directed more towards research and eradica tion of symptoms arising from already established cardiovascular morbidity than towards purely pre ventive measures For cerebrovascular morbidity the treatment of hypertension at this age has several preventive aspects (16) It is likely that in this age group there will be more cases of secondary hypertension than of the usual essential hyperten sion

STUDY POPULATION

Between Aug and Dec 1975 all men living in Uppsala and born in 1915 were offered a health examination Out of a population of 422 men 331 arrived Thus the participation rate was 78 4% The screening procedures have been described elsewhere (26)

Hypertension was defined as a diastolic BP (DBP) of 105 mmHg or more This limit was chosen to correspond with that of 50-year-old men in the same community (13) Pure systolic hypertension (SHT) was studied separately in a further group not included in the other hypertensive groups and was named SHT group comprising men with a systolic BP (SB) of ≥175 mmHg and a DBP of <105 mmHg None of the subjects in the SHT group were on antihypertensive treatment. Subjects who at the time of investigation were already on treatment for hypertension were also included in the hypertensive population

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Abbreviations BP = blood pressure DBP = diastolic BP SBP = systolic BP SHT systolic hepertension GFR = glomerular filtration rate ECG = electrocardiogram HR = heart rate C_{cr} = creatinine clearance

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Table I *Blood pressures (mmHg) and heart rates (beats/min) in treated and untreated hyperten the SHT group and in the remaining population sample (mean ± S D)*

	Hypertensives			Remaining population sample
	Treated (n=41)	Untreated (n=23)	SHT (n=10)	(n=257)
SBP	166 7±19 4***	177 0±21 9***	183 0± 9 5***	137 4±16 2
DBP	100 4± 9 3***	109 1± 4 4***	92 5±5 4***	82 9± 8 3
HR	64 6± 8 3	67 7±11 9	73 0±20 6	66 7± 9 8

***$p < 0\ 001$ compared to remaining population sample

METHODS

Blood pressure measurements

The BP and heart rate (HR) were recorded after 10 min of supine rest and the sitting BP was measured after another 2 min A mercury manometer (Kifa Ercameter wall mod el) with a rubber bladder (cuff 12 cm wide and 35 cm long) was used The BP was measured on the right arm and read to the nearest 5 mmHg The DBP was recorded at the disappearance of the Korotkoff sounds (phase 5)

The examination took place at 7 00–8 30 a m and all BPs were recorded by the same registered nurse who took part in the previous screening of 50-year old men (13)

Medical history

The medical history was obtained by means of a modified self administered questionnaire ad modum Collen and by a direct personal interview Information was gathered on hereditary aspects previous diseases drug intake smok ing habits and stress symptoms

nthropometric measurements

ight was measured without shoes and weight in under orts The heights and weights of the previously ex amined 50-year old men (13) were used as references for the relative body weight index The subscapular skinfold thickness was measured in the sitting position with a Harpender caliper (9)

Statistical methods

Conventional statistical methods were used in tl tion of mean and S D Significances of differenc mean values were estimated according to Stud (two tailed)

Laboratory investigations

The following laboratory investigations were p *Serum* haematocrit ESR glucose tri cholesterol albumin creatinine calcium urate gammaglutamyl transferase *Urine* Clinistix® volume per 24 h and 24 hour values potassium calcium phosphate magnesium ethyl alcohol Blood samples were taken in a fa A 24-hour urine sample was collected from 32 subjects entering the screening None of those collect urine had been diagnosed as hypertensi screening or had a resting DBP of ≥105 mmHg reduce possible errors caused by inadequately collections or variations in electrolyte excre body size or differences in glomerular filt (GFR) the values were related to the sim obtained 24-hour creatinine clearance (C_{cr}) formula given by Nordin et al (20)

A 12 lead resting electrocardiogram (EC corded in all participants Leads I II III aVF V_1–V_6 were used The ECGs were int

Table II *Anthropometric measurements and laboratory findings*

Body weight index is based on the findings in the 50-year old men in the same community (13)

	Hypertensives						Rem popu samp
	Treated		Untreated		SHT		
	Mean	S D	Mean	S D	Mean	S D	Mea
Body weight index	1 07***	0 09	1 06*	0 10	0 94**	0 07	1 0
Subscapular skin fold thickness (mm)	18 9***	8 2	14 3	5 6	13 7	8 2	13 4
Triglycerides (mmol/l)	2 3*	1 8	2 0	1 1	1 8	1 2	1 6
Cholesterol (mmol/l)	6 4	1 3	6 6	1 3	6 9*	1 2	6 1
Blood glucose (mmol/l)	5 4	2 0	5 0	2 0	5 7	0 7	5 4
Urate (µmol/l)	309 4**	65 5	267 8	59 5	238 0	41 7	267 8

*$p < 0\ 05$ **$p < 0\ 01$ ***$p < 0\ 001$ compared to remaining population sample

III *Correlations between BP and urinary excretion of sodium potassium calcium and magnesium made for endogenous creatinine clearance) in 24 hour samples*

	Untreated (n=23) (DBP)		Untreated + SHT (n=33) (DBP)		Population sample (n=135) (SBP)	
	r	p	r	p	r	p
ı	−0 372	<0 05	−0 248	<0 05	0 168	<0 05
um	−0 528	<0 01	−0 281	<0 05	−0 088	>0 05
n	−0 313	>0 05	−0 264	<0 05	0 053	>0 05
ıum	−0 251	>0 05	−0 342	<0 01	−0 147	<0 05

hysicians independently at the Department of l Physiology and coded according to the Minnesota 5)

RESULTS

ence of hypertension

ie personal interview and in the self istered questionnaire 41 men (12 4%) re d an established hypertension In addition at reening 23 men (6 9%) had a previously un resting DBP of 105 mmHg or more Thus the prevalence of hypertension was 19 3% Ac g to the WHO criterion ≥160/95 mmHg 116 35 0%) were hypertensive

art rate and treatment for high BP

ean SBP was 166 7 mmHg in the previously d group (n=41) and 177 0 mmHg in the un d group (n=23) (Table I) These values were antly higher (p<0 001) than the mean value 4 mmHg in the remaining population sam =257 excluding the SHT group) The mean as also significantly higher (p<0 001) in the hypertensive groups than in the population sample The distribution of the BPs among the total age group has been reported elsewhere (26) From this it may be noted that 10 3% had a SBP of ≥175 mmHg and 6 9% had a DBP of ≥110 mmHg

The mean HR was very similar in the treated untreated and SHT groups though the treated hypertensives had a somewhat but not significantly lower mean value The SHT group had a mean resting HR of 73 beats/min Twenty five men were being treated with β blocking agents either as a single drug or in combinations 11 were on saluretic treatment alone Twenty three men (56 1%) who had a DBP of <105 mmHg at screening were considered to be adequately controlled

Other information from questionnaires and interviews

Slightly more than twice as many men in the treated group than in the remaining population sample reported that their fathers had died from myocardial infarction The prevalence of reported hypertension was also significantly higher amongst fathers and

IV *Occurrence (%) of ECG abnormalities according to the Minnesota code (23) (Roman numerals) subjects had more than one abnormality)*

	Hypertensives			Remaining population sample (n=257)
	Treated (n=41)	Untreated (n=23)	SHT (n=10)	
logical ECG	26 8	17 4	40	12 8
ems (I)	2 4	–	10	1 6
S axis deviation (II)	9 8	8 6	–	1 9
h QRS amplitude (III)	9 8	8 6	10	2 7
depression (IV)	7 3	8 6	10	1 9
ave items (V)	19 5	8 6	30	6 2
conduction defects (VI)	2 4	4 3	–	0 4
ntricular conduction defects (VII)	2 4	–	–	1 9
ythm (VIII)	4 8	4 3	20	4 7
cellaneous (IX)	–	4 3	–	1 2

Table V *Comparison of BP levels (mmHg) and HRs (beats/min) in 50 and 60 year old men in l (mean±S D)*

	50-year-old men		60-year-old men	
	Total population (n=2322)	Remaining population sample (n=1988)	Total population (n=331)	Remaining population sample (n=257)
SBP	133 2±18 1	131 5±16 5	145 2±22 4	137 4±16 2
DBP	83 7±11 2	82 7±10 2	87 2±11 6	82 9± 8 3
HR	68 9±10 7	68 4±10 4	66 7±10 3	66 7± 9 8

brothers of the men in the treated and untreated groups than in the remaining population sample

Angina pectoris diagnosed by a physician was reported by 19 5% in the treated group and by 10 1% in the remaining population sample Three men (30%) in the SHT group had angina pectoris

In the group of untreated hypertensives nine had consulted a physician for various reasons during the year of the screening and seven during the year before (1974) Nineteen had attended the general *health examination the last time they were called* Twelve of the 19 were considered then to be hypertensives

In the previously treated group 11 men (26 8%) stated that they often felt stressed The correspond ing figures for the group with previously unknown hypertension and for the remaining population ere 7 (30 4%) and 39 (15 2%) respectively

Twelve men (29 3%) in the treated group and four (17 3%) in the untreated group were smokers There were no differences between the adequately treated hypertensives (n=23) and the treated group (n=18) with a DBP of ≥105 mmHg with regard to the occurrence of other diseases stress symptoms or smoking habits

An increase in body weight by more than 10 kg since the age of 30 was noted by 17 men (73 9%) in the untreated group and by 19 (46 3%) in the treated In the remaining population sample 75 men (29 1%) reported such an increase

Anthropometric measurements

The treated group had a relative body weight index of 1 07, which was significantly higher (p<0 001) than in the non hypertensive population sample (Table II) In the untreated group this index was 1 06 which was also higher (p<0 05) than in the non hypertensive sample The SHT group had an index of 0 94 which was significanth (p<0 01) than in the non hypertensive sam

Laboratory investigations

Serum measurements Serum urate was pected significantly higher (p<0 01) in th group than in the non hypertensive p sample (Table II) The serum triglycer cholesterol values were all higher in the h sives than in the non hypertensives

Urine measurements The correlations BP and urine electrolytes are given in Tal positive significant correlation was found supine SBP and urinary sodium (r=0 168 in a group of 135 healthy men (with n disease or medication) These 135 subje selected at random from participants in t screening of 60-year old men fulfilling th mentioned In the group of untreated hyp a negative significant (r=−0 372 p<0 0 tion was found between sitting DBP an sodium A negative significant correla −0 528 p<0 01) was found between urin sium excretion and sitting DBP in the gro treated hypertensives When the SHT the untreated group were combined (n= same pattern was again noted with negativ tions between sodium and potassium exc the urine and sitting DBP (Table III) A correlation was found between sitting DBP nary excretion of calcium (r=−0 264 p<(magnesium (r=−0 342 p<0 01) in the c group

Alcohol was detected in the urine of (11 0%) in the total material and in 22 0 treated hypertensives There was no signifi ference in the mean BP level between the treated hypertensives with alcohol in the u the remaining treated hypertensives

Gs were considered pathological in 26 8% of eated hypertensives and in 40% of the SHT (Table IV)

DISCUSSION

of the purposes of this study was to com the 60-year-old men with their 50-year-old erparts The typical BP development to a r mean SBP in the older age group was found i SBP 145 2 and 133 2 mmHg respectively) ver the DBP values were nearly identical e V) This finding is in accordance with many reports (3 5 10 14 19 22 23 29) Care must ken however when comparing absolute BP s between various studies and it is preferable ow up one group of subjects over the years In esent comparison however some of the pos errors could be excluded For instance the urements were performed by the same nurse the same facilities in the same outpatient

et al (3) have shown that the average SBP in males between 15 and 25 years of age It seems to remain stable until the age of 44 it rises again until the age of 60 and then off Nicol and Little (19) also found that there o further increase in BP beyond that age finding of a lower mean HR ($p<0\ 01$) in the uning population sample and among un d hypertensives in the 60-year-old group than g 50-year-old men is of interest For the tensives it might be explained by a change in ypertensive pattern such as from a high ac output stage to a predominance of increased heral resistance Another explanation might be eral decrease in the rate of the sinus node with

was further considered of interest to make a ate study of men with a systolic hypertension (SHT group) Although very small ($n=10$) this p deviated from the others in some respects the mean serum cholesterol ($p<0\ 05$) and d glucose levels ($p>0\ 05$) in the SHT group higher than those in the remaining popula sample as well as in the other hypertensive ps The mean body weight was lower In addi we noted a relatively high share of pathological Gs Most likely the high SBP in this subgroup is mptom of an already manifested artherosclerot isease The above findings are in accordance with the report by Kannel (14) that even isolated SHT is a powerful predictor of morbidity and mor tality

Previous studies (1 13 21) have convincingly shown that the majority of individuals with high BP are either undetected or inadequately treated In this study 35 9% of the hypertensive population had not been detected before In the previously treated group 43 9% were poorly controlled Thus 64 1% of the total hypertensive population were either undetected or poorly controlled This high rate is not encouraging considering that many of these men had been investigated under other circumstances prior to the screening This points to the necessity of further intensified education among the public as well as among all medical professionals dealing with BP measurements

In this study the heredity showed a dominantly male line among treated hypertensives where as among the 10 year younger men the treated hypertensives mainly reported hypertension among mothers and sisters Further a higher proportion of men in the treated than in the untreated group among the 60-year-olds gave positive information on heredity The reason for this is probably that hypertensives already under treatment have had more regular contact with a physician

There appears to be a higher proportion of indi viduals with a weight gain of more than 10 kg since the age of 30 among hypertensives than in the gen eral population It would therefore seem to be a risk factor for hypertension The possibility that the in crease in weight is secondary to the hypertension per se cannot be totally ruled out

Another purpose of the present report was to study the urinary content of alcohol and the excre tion of some electrolytes Alcohol has been shown to increase BP levels (7 11 25) Waern et al (27) found that the mean SBP and DBP levels were somewhat higher ($p>0\ 05$) among 60-year-old men showing various indications of alcohol consump- tion However increased alcohol intake could also represent increased caloric intake and thus increased BP might be a function of increased body weight However in the treated group alcohol in the urine did not seem to affect the hypertension In the group of untreated hypertensives who at the screening examination were informed of their high BP none had alcohol in the urine on the following day This could have been fortuitous but it might also be related to the BP examination result

When measuring various electrolytes in a 24 hour urine sample the reliability of the subject in making a complete collection is critical For practical reasons it was not possible to collect urines in duplicate in this health examination The urinary electrolyte excretion was therefore multiplied by a correction factor C_{cr} namely the endogenous creatinine clearance Wibell and Bjorsell Östling (28) state that in good collectors endogenous creatinine clearance corresponds well with GFR at various ages In large materials Healy (12) reported a linear regression between inulin clearance and C_{cr} thus making it possible to use C_{cr} in estimates of GFR Having corrected the electrolyte excretion as mentioned above and knowing that the proportion of poor collectors was low the results should be reliable The urinary electrolyte pattern has been studied previously in unselected health populations only with special regard to sodium (2) It is natural that this electrolyte has received most interest in view of its close relationship to the pathogenesis and maintenance of hypertension There are reasons however for studying other electrolytes particularly as many antihypertensive drugs influence their excretion and might thus induce side effects The effect of some saluretics on magnesium for example (8), needs further investigation We studied therefore individuals of the same age and sex whose BP represented the whole spectrum from w to high aiming at detecting any abnormal han ing of electrolytes by the hypertensive kidney

We found a positive and significant correlation between the excretion of sodium and the SBP in the group of men with no known disease or medication However in the group of untreated hypertensives there was a tendency towards a negative correlation Similar findings concerning sodium excretion have been reported by Berglund et al (2) A possible explanation for this handling of sodium by the kidneys is that up to a certain BP level there is a pressure diuresis, and at higher BP levels the kidney retains electrolytes Brown et al (4) and Schalekamp et al (24) have explained the deterioration of the renal ability to excrete sodium as secondary to an increased renovascular resistance The results of our study seem to indicate that the kidneys are handling the other electrolytes in the same way

The advantages of screening for hypertension at the age of 60 might be regarded as dubious But according to figures published by Metropolitan Life Insurance Company (15) therapeutic gains achieved even in these age groups Thus expectancy for males at the age of 55 is red 6 years if the BP is 150/100 mmHg Treat hypertension at this age might also be of reducing cardiovascular symptomatology as the incidence of cerebrovascular disease

A further reason for screening for hyperte 60 year olds is the assumption of an increa valence of secondary hypertension Thus et al (17) found such a trend in their 2422 hypertensives Arteriosclerotic reno hypertension increased in their study from the age group 21–30 years to 33 4% in t years group Screening at the age of 60 will reveal more cases of secondary hyperten screening at 50 years

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The Effects of a $Beta_1$-Blocking Agent, Atenolol, on Blood Pressure, Plasma Renin Activity and Prostaglandin $F_{2\alpha}$ Excretion in Patients with Essential Hypertension

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ACT The antihypertensive action of β block nts has been suggested to be associated with rease in plasma renin activity (PRA) and can agonized by indomethacin, a prostaglandin nthesis inhibitor We studied the acute and rm effects of a β_1 blocking agent, atenolol b i d), on blood pressure (BP), PRA and $PGF_{2\alpha}$ excretion in 12 male patients (40 ld) with essential hypertension BP was meas y means of a brachial cuff PRA and $PGF_{2\alpha}$ timated radioimmunologically One day after tiation of atenolol treatment BP fell signifi the supine values from 159/114 to 143/104 and the erect from 158/118 to 140/106 mmHg weeks BP decreased further to 135/94 and mmHg, respectively After the cessation of l for three weeks BP rose to the pre atenolol hen the dose was readjusted (25–150 mg daily weeks), diastolic BP remained at 100 mmHg or in only two patients During the atenolol nt PRA declined to one third of the pre l level in one day and to one half in six weeks inary excretion of $PGF_{2\alpha}$ was not affected by l Our results suggest that 1) the antihy sive action of atenolol and the reduction of re substantial already in one day, and 2) the se in BP or PRA is not associated with $PGF_{2\alpha}$ tion

ords atenolol beta adrenergic blocking agents renin activity prostaglandin excretion hyperten

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adrenergic blocking agents are widely used in eatment of essential hypertension (6 28 29) olol is a β_1 selective blocking agent which is d of intrinsic sympathomimetic and membrane stabilizing action (4 5) Its antihypertensive effect is also well documented (3 7 16 17 23 24) The mechanism of the antihypertensive action of β blocking drugs is still unclear in detail but decrease in cardiac output effects on the central nervous system and inhibition of the renin–angiotensin system have been suggested (6 35) Recently the antihypertensive action of β blocking drugs has been reported to be substantially antagonized by a prostaglandin (PG) synthetase inhibitor indomethacin (8 9) Thus PGs may also be involved in the antihypertensive action of β blocking agents

In order to investigate the antihypertensive action of β_1 blocking drugs in detail we studied the acute and long term effects of atenolol on blood pressure (BP) heart rate (HR) plasma renin activity (PRA) and electrolyte excretion in patients with essential hypertension It has been found previously that indomethacin decreases $PGF_{2\alpha}$ excretion in hypertensive patients in close relation with PRA (36) and most probably also reduces PGE excretion (12) Since the determination of $PGF_{2\alpha}$ with our methodological facilities is more reliable than that of PGE and evidence has been presented that $PGF_{2\alpha}$ exhibits an excretion pattern similar to PGE (15 33) we have measured the excretion of $PGF_{2\alpha}$ also in the present study in order to obtain infor

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Abbreviations PG = prostaglandin PRA = plasma renin activity BP = blood pressure HR = heart rate Na^+ = sodium K^+ = potassium

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Fig 1 Design of the trial

mation on the action of atenolol on renal PG biosynthesis The side-effects of atenolol were also taken into consideration

STUDY POPULATION AND METHODS

Patients

Twelve male patients were studied All had diastolic arterial pressures of at least 110 mmHg in health screening examinations arranged in Tampere Finland for men aged 40 years In seven (58%) of the 12 patients high BP values had been measured 1–12 years previously However none of the 12 patients had been treated with antihypertensive agents during the last six months All the patients were aware of their participation in the study They were asked to continue their ordinary life over the whole study period without any dietary restriction except for abstaining from alcoholic beverages and fasting on the mornings of visits to the Outpatient Hypertension Clinic

Measurement of BP

The diagnosis of arterial hypertension was confirmed at the two initial visits to the Outpatient Hypertension Clinic of the Community Health Centre of Tampere During the trial BP was measured at an interval of three weeks between 8 50 and 9 20 a m first at rest after lying down for min and then erect after standing for 2 min two meas being made in each position Diastolic BP was at the fourth Korotkoff sound HR was counted y BP was measured by one and the same physician at the same time on the same weekday in the right arm with the same brachial cuff and mercury manometer with an accuracy of 2 mmHg The lowest of the two measurements was used for analyses When the patients were treated with placebo or atenolol they took their drugs 2 5 h before the BP measurement

Examinations

The following examinations were performed for the discovery of possible complications of the disease and for the exclusion of secondary hypertension careful physical examination inspection of the ocular fundi ECG and chest X ray with estimation of heart size Eleven patients (92%) had 1st or 2nd degree hypertensive changes in the ocular fundi Left ventricular hypertrophy was found in three patients by ECG and in one patient by chest X ray These four men (33%) were classified as WHO stage II The laboratory examinations were as follows ESR haematocrit Hb erythrocytes mean corpuscular Hb mean corpuscular Hb concentration mean corpuscular volume reticulocytes leucocytes differential leucocyte count platelets prothrombin time (estimated by Simplastin A) serum creatinine serum aspartate and alanine aminotransferases serum alkaline phospha glucose serum antinuclear antibodies serum N urinary protein glucose sediment and bacte They were determined just before and six week beginning of atenolol treatment The did not reveal any signs of secondary hyperten

Design of the trial (Fig 1)

After a period of three weeks without any patients received placebo (single blind) for one tablet b i d Thereafter a fixed dose of atenolol was given b i d (at 6 20 or 6 50 a.m for six weeks followed by 3 weeks without treatment Finally the patients received ate further 26 weeks the doses being adjusted (25–150 mg daily) Atenolol tablets were sup Ltd Tampere

PRA urinary excretion of $PGF_{2\alpha}$ and ser nary Na^+ and K^+ were measured five times course of the trial before and after the plac one day and six weeks after the beginning treatment and three weeks after withdrawal Serum Na^+ and K^+ were re-examined twice additional atenolol treatment for 26 weeks

Determinations of PRA $PGF_{2\alpha}$ and electroly

For the estimation of PRA venous blood sa drawn from the patients sitting at rest for before the BP measurement) into cooled test taining 0 1 N Na_2EDTA $PGF_{2\alpha}$ Na^+ and K were determined in urine collected over th night for 12 h corresponding to the dose placebo or atenolol Plasma and urine sampl 33% alcohol solution for the $PGF_{2\alpha}$ stored at −20°C until analyzed

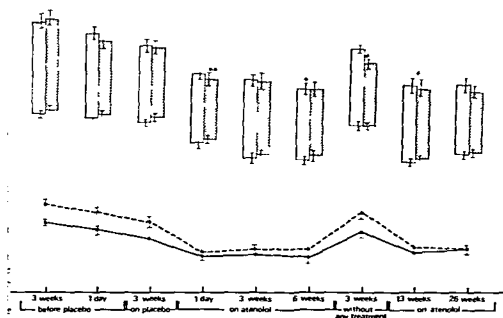
PRA was determined in the Minerva Institu cal Research Helsinki by radioimmu giotensin I released in incubation as describ quist et al (13) $PGF_{2\alpha}$ was extracted by Unger et al (27) and measured radio Antigen–antibody complex was separated by of Gersham et al (14) Recoveries were using labelled PGE_1 (sp act 53 Ci/mmol Centre Amersham) The cross-reactivity of antiserum was less than 0 02% with PGE PC Serum and urinary Na^+ and K^+ were photometry

Side effects

During the periods with or without active the subjective symptoms or side-effects were active questioning and graded from I to III (m ate severe) New symptoms during were recorded separately

Statistical methods

The mean values ± S E were calculated The di between the means were evaluated by paired gression equations were calculated by the method squares



BPs and HRs (mean±S E) prior to and during treatment of 12 male patients with essential ...sion The columns represent systolic (tops) and (bases) BPs in supine (□) and erect (□) position —=Supine HRs =erect HRs *$p<0.05$ ** $p<0.01$ *** $p<0.001$ as compared to the preceding BP or HR values

RESULTS

...ressure and heart rate

...vas no significant decrease in BPs between ...visits before the placebo period (Fig 2) ...an systolic and diastolic BPs in supine posi... ...reased slightly during the placebo period ...4/117 to 159/114 mmHg ($p<0.05$) ...e day after the beginning of atenolol treat... ...our of the patients became normotensive ...lic BP fell below 100 mmHg in both posi... Compared to the BP during the placebo ... the mean values of supine and erect BPs ...ed to 143/104 and 140/106 mmHg respec... $p<0.01$) The corresponding decreases in ...e from 72 to 60 and from 78 to 61 beats/min ...eeks BP decreased further supine to 135/94 ...ect to 134/96 mmHg and five additional pa... ...ecame normotensive Also the supine HR ...tended to decrease further When atenolol ...n withdrawn in all the patients the BP and ...ues rose in three weeks to the pre atenolol ...o symptoms of withdrawal effect were ob...

...ng an additional period of 26 weeks on atenolol BP and HR decreased to the level before the drug discontinuation In three patients the doses of atenolol could be reduced to 50 mg and in one to 25 mg daily without any notable reduction in the antihypertensive responses In two patients the dose was raised to 150 mg daily but one of them and another patient receiving 100 mg atenolol daily still remained hypertensive (diastolic BP 100 mmHg or more in both positions) at the close of the trial Thus a good antihypertensive effect was obtained in 83% of the cases

Plasma renin activity and prostaglandin $F_{2\alpha}$ excretion

There was no significant difference between PRA values before and after the placebo period (Table I) During the atenolol treatment PRA decreased in one day to almost one third of that on placebo Six weeks later PRA values were still lower than during the placebo treatment but higher than those measured one day after the beginning of the atenolol therapy ($p<0.05$) When atenolol was discontinued PRA increased almost to the pre atenolol level No correlations between the falls in BP and PRA were

Table I *Action of atenolol (50 mg b i d) on PRA PGF$_{2\alpha}$ excretion ratio PRA/PGF$_{2\alpha}$ excre on \ K$^+$ excretion urine volume and serum Na$^+$ and K$^+$ in 12 male patients with essent al hype (mean±S E)*

	Before placebo	3 weeks on placebo	1 day on atenolol	6 weeks on atenolol	3 week r withdraw of a eno
PRA (ng AI/ml×h $^{-1}$)	1 13+0 35	1 01+0 28	0 38+0 05*	0 54+0 11*	0 81 0
PGF$_{2\alpha}$ excret on (μg/12 h)	1 65+0 43	1 17+0 17	1 35+0 24	1 28+0 27	1 31 0
PRA/PGF$_{2\alpha}$ ratio	0 74+0 11	0 91+0 19	0 44+0 11*	0 77+0 30	0 86 0
Na excretion (mmol/12 h)	126 9±14 0	132 6+8 9	126 6+14 4	116 7+15 4	139 1 C
K excretion (mmol/12 h)	34 3±3 4	32 3+2 8	32 3+3 6	27 2+3*	36 3
Urine volume (ml/12 h)	691+62	711+56	702+51	573+54	641 ſ
Serum Na (mmol/l)	140 8±0 7	141 5+0 5	140 0+0 5*	139 6+0 6 **	139 8+1
Serum K (mmol/l)	4 2±0 1	4 3+0 1	4 4+0 1	4 3+0 1	4 3 0

*$p<0.05$ ***$p<0.001$ as compared to values on placebo

found in single patients either one day or six weeks after the beginning of the atenolol treatment except between the falls in the erect diastolic BP and PRA after the six week atenolol treatment (r 0 665 $p<0.05$) Three weeks after the withdrawal of atenolol the individual increases in systol c or d astolic BPs in supine or erect posit ons did not correlate either with the rises in PRA However when the correlation coefficients between the total of all measured PRA values ($n-58$) and correspond ing BPs were determined the erect systolic BP val ues and the diastolic pressures in both positions correlated significantly to PRA (r 0 284–0 474 $p<0.05$–0 001)

There were no significant changes in PGF$_{2\alpha}$ ex cretion during the course of the trial The 12 hour urine of one patient was contaminated with semen and the corresponding PGF$_{2\alpha}$ excretion value was exceptionally high Consequently all the PGF$_{2\alpha}$ excretion values of this patient were excluded The ratio PRA/PGF$_{2\alpha}$ excretion decreased substantially in one day during the atenolol therapy but no more six weeks later

Electrolytes

During the atenolol therapy serum Na$^+$ decreased slightly but significantly in six weeks (Table I) Af ter discontinuation of the drug it d d not however return to the pre atenolol level During additional treatment with atenolol for 26 weeks there were no significant changes in serum Na$^+$ (140+0 5 and 141±0 5 mmol/l two measurements performed) as compared to the concentration on placebo Serum K remained unchanged through the periods with and without atenolol also during the additional drug period of 26 weeks (4 4+0 1 and mmol/l) The urinary K excret on declin weeks on atenolol treatment and increase when atenolol was discontinued Both the cretion and the urine volume tended to d during the six week period on atenolol T body weight decreased by 2 kg during the and remained at the reduced level even th three week period without atenolol

Other laboratory parameters

The various other laboratory parameters show any s gnificant changes during atenol ment except for a sl ght increase in pro time ($p<0.05$) from 0 75±0 02 to 0 84+ mated by S mplastin A)

Side effects

The total number of patients with subject toms and the number of complaints wer h ghest 9 and 19 respectively in th before placebo against 7 and 10 during the period They were of the same order of in the atenolol periods up to six weeks creased again after withdrawal of the d atenolol treatment was reinstituted for tw periods of 13 weeks only one or two exhibited together one or two symptoms

Only one patient had a new symptom (dr on the first day on atenolol Two pat ents h new symptoms (weakness of legs dry mo ziness and sl ght diarrhoea) and two pat new symptoms (dry mouth and cold ext during the following two treatment period weeks respectively After d scontinua

ol for three weeks the number of new symp- ncreased again five new symptoms in five s No new side effects appeared when ol treatment was reinstituted for a further 26 as compared to the complaints during the without atenolol

DISCUSSION

itient population of the present study was homogeneous one consisting of middle aged therwise healthy with established essential nsion None of them had received any ertensive treatment during the last six in most cases never at all or not for many

e was a marked fall in the systolic and c BPs already one day after the initiation of l treatment A decrease in BP in one day een reported also when e g pindolol or olol was used (34) Atenolol and pro- l have been found to reduce BP substan during three days of treatment (20 21) ant decreases in systolic and diastolic BPs cently found in healthy volunteers already and 4 h respectively after administration of l orally (100–200 mg) the decrease in BP still being apparent 8 h and in diastolic after administration (11) The β blocking e g atenolol reduce HR and consequently iac output (22) which would partly explain d fall in BP

was also a substantial decrease in PRA uring atenolol treatment In this study PRA easured in sitting patients without any restriction on their food intake or normal e this situation better corresponded to their y life conditions than e g recumbency or restriction before sampling In spite of that ults are in agreement with the previous tions of falls in PRA caused by atenolol (1 26) In general there was only a poor tion between the decreases in BP values and renin levels in the individual patients during l treatment and withdrawal of the drug did ult in any correlation between the increases and PRA No correlation between these ters has been found in some other studies 2 10 20) The changes in PRA by atenolol ot been found to correlate either with plasma ol concentrations or changes in BP values in supine or erect positions or during exercise (23) In addition in this study PRA increased slightly during the course of the atenolol treatment but BP decreased further The above observations counteract the idea that the reduction in BP is dependent on PRA alone On the other hand when the BP values fell during atenolol treatment the PRA values also fell and significant correlations were found between all the PRA values and the corresponding erect systolic BPs or the diastolic pressures in both positions This suggests that the changes in BP caused by β_1 blocking drugs at least partly occur concomitantly with the alteration in PRA (19)

Indomethacin treatment markedly suppresses $PGF_{2\alpha}$ excretion by inhibiting biosynthesis of PGs This is closely accompanied by the decrease in PRA (36) In the present study $PGF_{2\alpha}$ was unaffected by atenolol but PRA was substantially decreased This suggests that the decrease in PRA does not necessarily result in a reduction in $PGF_{2\alpha}$ production although the opposite dependence between these parameters may exist Evidence has been presented that $PGF_{2\alpha}$ has an excretory pattern similar to PGE_2 another common renal PG (15 33) Urinary $PGF_{2\alpha}$ may thus at least to some extent reflect the overall excretion of PGs It cannot however be excluded that the production of other members of PG series e g PGI_2 and PGG_2 which stimulate the renin release (31 32) may be changed by β blocking drugs

There was a significant decrease in K^+ excretion *during the atenolol therapy Thus atenolol seems* to spare K^+ as other β blocking agents e g metoprolol may also do (30) although we did not find any significant increase in serum K^+ It is likely that this reduction in K^+ excretion was due to the tendency of urine volume to decrease during atenolol treatment A similar tendency was found in Na^+ excretion but unexpectedly the serum Na^+ concentration also decreased statistically significantly in six weeks This decrease is however without marked biological significance especially since the discontinuation of atenolol treatment for three weeks did not cause an increase in serum Na^+ and during an additional atenolol period of 26 weeks serum Na^+ no longer differed from the values before atenolol In spite of a tendency towards reduced diuresis the body weight of the patients decreased Thus there was obviously no marked fluid retention The discontinuation of atenolol for three weeks caused no renewed rise in body weight sug

gesting that the patients were aware of their disease and readjusted their dietary habits

The side effects of atenolol were few and slight All of the patients completed the trial and they still (about one year after the close of the trial) continue with the atenolol treatment

The results indicate that atenolol decreases systolic and diastolic BP HR and PRA in only one day and its antihypertensive effect becomes more marked during the following weeks Atenolol has no effect on $PGF_{2\alpha}$ excretion The falls in BP and PRA are not associated with the excretion of $PGF_{2\alpha}$ but we cannot exclude the possibility that atenolol may have some action on the excretion of some other members of the PG series

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The Dιagnostιc Challenge of Left Atrιal Myxoma

Importance of Echocardιographιc Screenιng

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ACT Left atrιal myxomas are extremely dιf dιagnose sιnce their varιable manιfestatιons host of clιnιcal entιtιes more commonly seen tral stenosιs endocardιtιs rheumatιc fever, ιyopathy or mesenchymosιs At the same ırly dιagnosιs followed by prompt surgιcal l are mandatory to prevent mutιlatιng or le nplιcatιons of the tumor Sιx cases of left yxoma were dιagnosed ιn our hospιtal durιng s We present the case hιstorιes, dιagnostιc ıres and surgιcal fιndιngs, consolιdatιng the role of echocardιography ιn detectιng left ıyxomas We propose the use of echocardιo- as a screenιng examιnatιon for atrιal myxo- the followιng settιngs suspected mιtral ob e dιsease, suspected endocardιtιs wιth negatιve ıltures, perιpheral embolιsm or thrombosιs ιn patιents unexplaιned cardιac faιlure and ιymosιs wιth uncharacterιstιc presentatιon

ds left atrιal myxoma dιfferentιal dιagnosιs ɔgraphy screenιng
ɟ Scand 206 115 1979

ıas are known for theιr masqueradιng fea ıresentιng wιth obstructιve embolιc or con nal symptoms ιn varyιng combιnatιons (5 Apart from mιtral stenosιs and arterιal ɔm dιagnoses lιke endocardιtιs rheumatιc nesenchymosιs and cardιomyopathy are fre ׳ suspected before a defιnιtιve dιagnosιs of ıa ιs establιshed by catheterιzatιon opera autopsy (9 13 14 18 25)
e the early reports documentιng the feasιbιlι hocardιographιc detectιon of left atrιal myx ɔy Effert and Domanιg (2) ιn Germany and (1) and later Holm and Hennιngsen (10) ιn navιa more recent papers have appeared mendιng echocardιography as a valuable screenιng procedure ιn thιs settιng (4 15 22 26 27)

Durιng the last 2½ years we have dιagnosed sιx cases of left atrιal myxoma We report the clιnιcal features and dιagnostιc procedures regardιng these cases wιth the aιm of consolιdatιng the role of echocardιography as a unιque screenιng procedure promptιng early detectιon and treatment of myx omas

PATIENTS

From Sept 1975 to Aprιl 1978 sιx patιents were operated on ιn our hospιtal for left atrιal myxoma Age sex clιnιcal and laboratory data are summarιzed ιn Table I Only one patιent (no 4) was suspected of a left atrιal myxoma on clιnιcal grounds alone Clιnιcal suspιcιons precιpιtatιng precatheterιzatιon referral to ultrasound examιnatιons are shown ιn Table II One patιent (no 1) however was not examιned by echocardιography

CASE REPORTS

Patιent 1

A 55 year old woman wιth a hιstory of prevιous rheumatιc fever and dyspnea on effort The characterιstιc fιndιngs of mιtral stenosιs and regurgιtatιon were notιced on physιcal examιnatιon (Table I) The dιagnosιs was confιrmed at rιght and retrograde left heart catheterιzatιon wιth left ventrιcular angιography Echocardιography was not avaιlable at the tιme of ιnιtιal dιagnosιs Before the scheduled operatιon the patιent was readmιtted wιth symptoms of ιncreasιng dyspnea and fever Hyper sedιmentatιon and anemιa were now present Short ly before and durιng thιs admιssιon the patιent experι enced several syncopes A dιagnosιs of recurrent rheu matιc fever or endocardιtιs was suspected and the patιent was treated wιth penιcιllιn despιte negatιve blood cultures At operatιon a 3×4×5 cm pedunculated left atrιal myxoma was found The postoperatιve course was uneventful In retrospect the myxoma ιn the left atrιum was faιntly seen on the left ventrιcular angιogram

Table I *Clinical and laboratory findings in 6 patients with left atrial myxoma*

All patients had sinus rhythm
DM = diastolic murmur SM = systolic murmur S_I & S_{II} = first and second heart sounds Hb = blood he[...]
centration SR = sedimentation rate

Pat no	Sex	Age (y)	Presenting symptoms	Auscultation	Pertinent laborat
1	♀	55	*Dyspnea fever syncopes*	*Accentuated S_I & S_{II}* opening snap SM & DM	*Hb↓ SR↑ bk* cultures nega
2	♂	42	Dyspnea fever fatigue loss of weight arthralgias palpitations	Accentuated S_I & S_{II} protodiastolic gallop DM	Hb↓ SR↑ S γ-globulin↑ cultures nega
3	♀	38	Dyspnea fever loss of weight	Accentuated S_I & S_{II} protodiastolic gallop SM	Hb↓ SR↑ S γ-globulin→ cultures nega
4	♂	32	Recurrent arterial embolism (cerebrum retina legs)	Normal sounds no murmur	Hb→ SR→
5	♂	61	Relentlessly progressing refractory heart failure fever	Tachycardia friction rub no murmur	Hb→ SR→
6	♂	52	Dyspnea fever arthralgias exertional dizziness	Accentuated S_I & S_{II} inconstant DM no gallop	Hb→ SR↑ S γ-globulin→ cultures neg

Patient 2

A 42 year-old man with a one year history of increasing dyspnea, loss of weight fatigue arthralgias and fever Accentuated first and second heart sounds were heard on auscultation A protodiastolic gallop was present The laboratory findings were compatible with a diagnosis of endocarditis but blood cultures were negative (Table I) The patient was referred to echocardiography suspected of cardiomyopathy The examination showed the pres- • of a left atrial myxoma This finding was confirmed heart catheterization with pulmonary angiography ι operation a 6×6×6 cm pedunculated myxoma was removed The postoperative course was uneventful

Patient 3

A 38-year-old woman with symptoms of cough dyspnea and loss of weight progressing over half a year At the time of initial admission to a local hospital she presented with fever and peripheral edemas The patient was in sinus rhythm First and second heart sounds were accentuated A grade 3/6 holosystolic murmur and a protodiastolic gallop were heard at the apex Anemia and hypersedimentation were present (Table I) Blood cultures were negative Mesenchymosis endocarditis myocarditis mitral stenosis and atrial septal defect were all suspected by different examiners In view of the equivocal findings the patient was referred to our laboratory for echocardiographic examination *The diagnosis of left atrial myxoma* was established by ultrasound (Fig 2) and confirmed by pulmonary angiography At operation a 3×3×5 cm pedunculated myxoma was found The postoperative course was uncomplicated

Patient 4

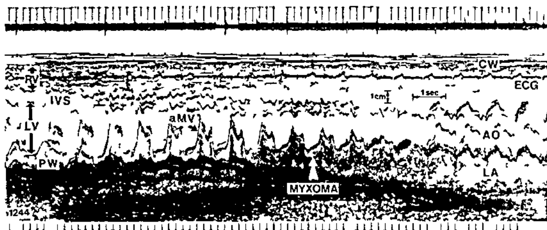
A 32 year-old man with recurrent arterial embolism during 2½ years *Suspected of increased thrombocyte aggrega*tion the patient was treated with antico[...] from embolism there had been neith[...] systemic manifestations (Table I) Ph[...] ECG chest X ray and laboratory data w[...] normal Nevertheless the *multiple em*[...] which had left the patient with a slight loss of visual acuity of one eye brough[...] a left heart myxoma and the patient [...] echocardiography The examination re[...] (2×2×3 cm) non-obstructing myxoma in [...] the left atrium (Fig 1) This finding wa[...] pulmonary angiography and operation [...] postoperative course

Patient 5

A 61 year-old man with relentlessly p[...] fractory bilateral heart failure associat[...] Treated with digoxin and diuretics withou[...] cardiologist at a late point of the course[...]

Table II *Suspected clinical diagn[...] echocardiographic examination or ope[...]*

	Pa
Mitral valve disease	1
Endocarditis	1
Myocarditis	?
Cardiomyopathy	2
Pericardial effusion	5
Atrial septal defect	3
Myxoma	4
Mesenchymosis	3
Pathological coagulation	4

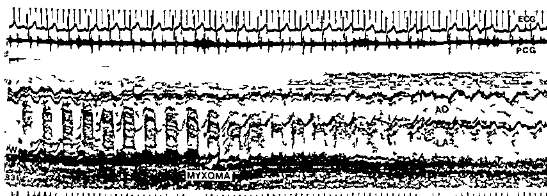


Representative M mode echocardiogram from pa demonstrating a small sessile non-obstructing apsing myxoma During recording the angulation *trasonic transducer has been changed continuous* a direction through the inferior part of the left (*LV*) near the apex to a direction intersecting of the heart represented by the aortic root (*AO*) left atrium (*LA*) Tumor echoes are seen in the inferior part of the left atrium behind the anterior mitral leaflet (*aMV*) throughout systole and diastole but do not enter the left ventricle reflecting small excursions of a *sessile tumor The motion pattern of the anterior mitral* leaflet is normal *CW* = chest wall *ECG* = electrocardiogram *IVS* = interventricular septum *PW* = posterior wall *RV* = right ventricle

severe distress A regular tachycardia was pres auscultation and a friction rub was heard (Table I) ial effusion with cardiac compromise was sus The echocardiographic examination displayed arge myxoma in the left atrium (Fig 3) Consider poor condition of the patient *no angiograms were* d At operation a huge (3 5×8×8 cm) peduncu myxoma occupying the greater part of the left and partially obstructing the pulmonary veins was the postoperative course was uncomplicated

Patient 6

A 52 year old man with a three year history of palpitations Progressing dyspnea had developed over half a year On heavy exertion the patient had experienced a few seconds of pronounced dizziness accompanied by temporary loss of vision *Proper syncopes had not been present* During three months there had intermittently been episodes of fever and arthralgias On admission the patient was in sinus rhythm and first and second heart sounds were accentuated A diastolic rumble was heard incon



M mode echocardiogram from patient 3 demon a moderate sized myxoma Recording obtained as *During systole* tumor echoes are seen in the left (*LA*) behind the inferior part of the aortic root During diastole the tumor echoes are seen in the ntricle reflecting the swinging motion of the tumor astolic motion of the anterior mitral leaflet is abnormal showing flattened or diminished diastolic closing rate suggesting obstruction of the mitral orifice The phonocardiogram (*PCG*) shows an *early diastolic sound* (tumor plop) occurring simultaneously with the maximal diastolic excursion of the myxoma Abbreviations as in Fig 1



Fig 3 M mode echocardiogram demonstrating large obstructing myxoma in patient 5 Tumor echoes are seen throughout the cardiac cycles in the visible part of the left atrium (also above the level of the aortic valves) reflecting a large tumor characterized by small excursions Only a minor part of the tumor is seen in the mitral ostium during diastole The diminished mitral valve ec the enlarged left atrium the small excursions of root and the very short ejection time as re aortic valve echogram signify severe ob the mitral orifice associated with low stro *Abbreviations as in Fig 1*

sistently at the apex but no gallop was noticed Slight hypersedimentation was present while all other laboratory tests were normal (Table I) Suspected of mitral valve disease the patient was referred for echocardiography which revealed a large mass occupying the visible part of the left atrium Pulmonary angiography confirmed the echocardiographic finding At operation a myxoma was successfully removed the tumor being ellipsoid (5×5×6 cm) and attached by a 3 cm broad base to the interatrial septum and prolapsing only partly through the mitral orifice The postoperative course was uncomplicated

DIAGNOSTIC METHODS

M mode echocardiography was performed using an Echoscan 30 equipment (Mediscan Denmark) with a 2 25 MHz transducer with 7 5 cm focus Recordings were obtained by means of a Cambridge Multichannel Physiological Recorder using photographic paper (Kodak Linagraph 1930) Several scannings from the left ventricle to the base of the heart or vice versa were obtained according to Feigenbaum (3) Care was taken to visualize the left atrium the mitral valve region and the left ventricle to obtain information on tumor extension mobility and degree of obstruction of the mitral ostium Patient 1 was not examined by echocardiography

Catheterization and angiography

Right and retrograde left heart catheterization with left ventricular angiography in 30° RAO (Urografin® 76%) were performed in patient 1 Patients 2–6 were examined by right heart catheterization only since the presence of a left atrial mass had been shown by echocardiography Pulmonary angiography (Urografin® 76%) in 30° RAO was performed in these patients This procedure was however omitted in patient 5 due to severe pulmonary hypertension and poor clinical condition

RESULTS OF DIAGNOSTIC METHODS

The diagnosis of left atrial myxoma was c (patients 2–6) or established (patient 1) d heart surgery Five patients (nos 2–6) r by echocardiography prior to catheter operation were all unequivocally diag having left atrial myxomas They were al upon within a few days after the ultraso before further complications occurred

No false positive diagnosis of myx made in the department during the perio but in one patient (no 1) a false neg graphic study was performed The ec graphic patterns of tumor localization or *aortic root and mitral valve movements* sistent with the findings of tumor locali and movements as evaluated by cathe angiography or operation (Table III)

Figs 1 2 and 3 respectively show ec graphic patterns of a small non-obstr non prolapsing tumor of a medium-s structing and prolapsing tumor and finally tumor almost occluding the left atrium ye protruding into the left ventricle during di

DISCUSSION

Despite their benign histological appeara omas usually induce a malignant disease c ized by progressing refractory cardiac fail lating or lethal embolism or sudden dea

III *Echocardiographic angiocardiographic and surgical findings*

tral valve EF slope (diastolic closing rate of mitral valve) LA left atrium LV=left ventricle MO=mitral orifice

Echocardiography	Angiocardiography	Surgery
Not performed	Left ventricular angiography mitral stenosis and incompetence (in retrospect prolapsing pedunculated tumor)	3×4×5 cm pedunculated tumor
EF<10 mm/sec systole tumor in LA diastole tumor in LV	Pulmonary angiography prolapsing pedunculated tumor	6×6×6 cm pedunculated tumor
EF<10 mm/sec systole tumor in LA diastole tumor in LV	Pulmonary angiography prolapsing pedunculated tumor	3×3×5 cm pedunculated tumor
EF>50 mm/sec systole tumor in LA diastole tumor in LA	Pulmonary angiography non prolapsing sessile tumor	2×2×3 cm sessile tumor
EF<10 mm/sec systole tumor in LA diastole tumor in LA & LV	Not performed	3 5×8×8 cm pedunculated tumor obstructing pulmonary veins
EF<10 mm/sec systole tumor in LA diastole tumor in LA & MO	Pulmonary angiography sessile tumor prolapsing partly through MO	5×5×6 cm sessile tumor

arly surgical removal of the tumor carries an nt prognosis and therefore early diagnosis atment are mandatory

ptoms and signs are frequently suggestive tually never diagnostic Due to the rarity of las and the highly variable clinical picture ommon cardiac diseases are usually sus Obstruction of the mitral ostium—the most n manifestation of left atrial myxoma—will be misdiagnosed as rheumatic mitral stenosis 8 9 14 18) The combination of sinus a short history of symptoms and a negative of rheumatic disease however should sug he possibility of myxoma (9) All our patients n sinus rhythm and with two exceptions (pa 4 and 6) the history was less than 1 year ng spells or endocarditis like symptoms l further support a suspicion of myxoma (pa) Arterial embolism may be the only manifes of a left sided myxoma (patient 4) and histo- l examination of peripheral emboli removed g surgery may occasionally be diagnostic (11)

presence of a pedunculated prolapsing left tumor swinging between the left atrium and ft ventricle is usually associated with a loud nged and delayed first heart sound at the time of ejection of tumor from the left ventricle to the left atrium and an early diastolic sound or protodiastolic gallop at the time of maximal prolapse of the tumor into the left ventricle (Fig 2) (12) Variable systolic and diastolic murmurs are heard depending on the degree of mitral regurgitation or obstruction of the mitral ostium When pulmonary hypertension develops the pulmonary component of the second heart sound becomes accentuated The auscultatory findings are often indistinguishable from those of rheumatic valvular disease However murmurs changing with position apparent late opening snap despite severe obstructive symptoms and low frequency indistinct character of the opening snap (tumor plop) are auscultatory features of potential help in differentiating mitral stenosis from left atrial myxoma (15)

In our cases auscultation appeared to be of limited value (Table II) Furthermore patients with myxomas need not at all have murmurs if stroke volume is very low (patient 5) or if tumor is very small and non-obstructing (patient 4) Prolapsing highly mobile tumors were characteristically associated with increased first heart sounds and early diastolic gallop in our series (patients 1 2 3) The degree of prolapse seems to be dictated not only by

the length of the pedicle by which the tumor is attached to the atrial wall, but also by the size shape and consistency of the tumor In patients 4 and 6 the tumor mobility was limited by a short and broad stalk In patient 5 the tumor though peduncu lated was impacted between the walls of the atrium and thereby restricted in motion The small and slow excursion of the tumors in these patients may explain the absence of an audible tumor plop

The combination of a cardiac murmur and con tinuous fever will—with or without concurrent arte rial embolism—often arouse suspicion of infectious endocarditis This diagnosis may be supported by laboratory evidence of anemia elevated sedimenta tion rate or changes in the concentrations of serum proteins as seen in our patients 1 2 and 3 Positive blood cultures do not exclude myxoma since left atrial myxomas may become infected (24) Even clubbing can be a sign of both endocarditis and myx omas (5 6 8 15 16 26) In this setting an echocar diogram can be of great help since scanning of the valves usually will distinguish between myxoma and valvular lesions due to the vegetations (3) al though mitral fungal vegetations in rare cases can be sufficiently large to mimic the echocardiographic picture of a left atrial myxoma (17)

When hypersedimentation anemia and hyper globulinemia occur associated with fever loss of weight Raynaud s phenomenon or joint pains the mary significance of cardiac manifestations may neglected and a diagnosis of mesenchymosis or rheumatic fever consequently suspected (patient 3) (7 13 25) Likewise the combination of cardiac signs and symptoms and constitutional manifesta tions may suggest a diagnosis of myocarditis or cardiomyopathy (patients 2 3) (21)

Occasionally the only obvious manifestation of a left atrial myxoma may be severe heart failure The absence of heart murmurs in that setting is probably due to low cardiac output (patient 5) (21 23)

Correct diagnosis will usually be made by means of catheterization and angiography (Table III) However the diagnosis may be missed if a left atrial myxoma is not specifically suspected as seen in one of our patients (no 1) and previously reported by others (15) Furthermore left sided heart cathe terization and particularly transseptal puncture is associated with risk of tumor fragmentation and embolism (14 19) Hemodynamic features of left atrial myxomas are variable Prolapsing tumors may be associated with increased c and v waves followed by rapid y-descents although l[...] insufficiency is present (16 20) These [...] changes were seen in three of our patien[...] 2 3) having highly mobile tumors but l[...] regurgitation Obviously pressure trac[...] specificity in diagnosing myxomas

Although the echocardiographic finding[...] atrial myxoma represent a spectrum th[...] pictures are seen reflecting tumor size an[...] (Figs 1 2 3 Table III) The echocardiog[...] patient 4 shows a small tumor (Fig 1) E[...] seen in the left atrium behind the anter[...] valve throughout systole and diastole but [...] the left ventricle The diastolic moveme[...] anterior mitral valve is normal indicating [...] tumor does not obstruct the mitral ostiu[...] cordance with this angiography and surg[...] onstrated a sessile non prolapsing non-[...] ing small myxoma attached to the low[...] septum

The echocardiograms from patients 2 an[...] the pattern of a moderate sized prolaps[...] (Fig 2) Echoes are seen in the left atrium [...] and in the left ventricular inflow tract durin[...] le thus suggesting the swinging motion of [...] mors (Table III) The diastolic closing ra[...] anterior mitral leaflet is reduced reflecting [...] tion of the mitral ostium Moderate sized p[...] lated highly mobile tumors were found [...] graphy and operation (Table III) The ech[...] grams from patients 5 and 6 show very larg[...] occupying the visible part of the left atriu[...] Tumor echoes are seen in the left atrium th[...] systole and diastole reflecting the small ex[...] of the myxomas Furthermore only min[...] the tumor are seen within the mitral fun[...] diastole At surgery a large sessile tumor w[...] in patient 6 while in patient 5 the tumor [...] pedunculated appeared to be restricted [...] due to the size of the myxoma (Table III)

Apart from the horizontal diastolic closi[...] the mitral valve associated echocardi[...] findings in patient 5 were poor excursio[...] aortic root and a very short ejection time [...] from the aortic valve echocardiogram ([...] signs of severely depressed stroke volume [...] findings were confirmed at catheterization [...] gery the large tumor impacted in the left at[...] found to obstruct not only the mitral orifice [...] the entrance of more of the pulmonary vein[...]

Thus regular correlations between echo[...]

c and hemodynamic/angiographic and surgi
ıdings obviously exist Based on our expe
and on previously published evidence we
ıt that systematic echocardiographic screen
r left atrial myxoma should be performed in
llowing settings 1) Suspected mitral obstruc
sease 2) Suspected endocarditis with nega
lood cultures 3) Peripheral embolism or
nbosis in young patients 4) Unexplained
c failure 5) Mesenchymosis with uncharac
: presentation Echocardiographic screening
ıents following these guidelines will secure
ıt correct diagnosis and treatment thus pre
g the serious complications of undiagnosed
nas

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Massive Embolization of Cardiac Myxoma

A Case Report

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TRACT A case of left atrial myxoma with mas embolization in a 20-year-old woman is de d The initial clinical picture was confusing but ited examinations including enzyme determina and arteriographies disclosed the presence of ple arterial emboli At embolectomy, histologi vestigation of embolic masses showed a picture ating cardiac myxoma This diagnosis was con d by pulmonary angiography and the tumour emoved Postischaemic oedema of the legs ne ated decompression operations The peripheral lation was restored and the final result was ex it Some aspects of the clinical presentation of incommon disease are discussed

ords cardiac myxoma arterial embolization post mic oedema fasciotomy

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ardiac myxoma is a rare tumour that occasion iay cause dramatic and confusing symptoms ive recently experienced a case of left atrial ma in a young woman presenting with leg ›s and subsequently offering some unusual ems regarding both diagnosis and treatment

CASE REPORT

viously healthy 20-year-old woman was suddenly ill with bilateral leg cramps while swimming As the ›s were quite severe and persistent she was brought spital without delay On admission to Sabbatsberg s ital on the evening of July 25th 1976 she complained infful muscular cramps in both legs and coldness in ft foot On examination however the dorsal arterial tions were palpable on both sides and the tempera of the feet did not differ Physical examination of the was normal and the BP was 100/90 mmHg Labora investigation revealed low levels of serum sodium mmol/l) and serum potassium (2 8 mmol/l)

the patient had been standing in the sun all day—one e hottest during that summer—a salt depletion syn ie (miner s cramps) was suspected She was accordingly treated with salt and fluid replacement but in spite of normalization of the electrolyte values the painful cramps persisted and she required repeated doses of seda tives and analgesics

During the following hours her condition deteriorated She complained of abdominal cramps nausea and vom iting An abdominal radiographic examination was nega tive Six hours after admission red urine was noted and was shown by laboratory analysis to be caused by myo- globin Furthermore CPK and liver enzymes (ASAT and ALAT) were greatly elevated A repeat examination of the legs now disclosed that the circulation in the left leg had deteriorated and that the pulse of the left femoral artery could no longer be palpated An arteriography was immediately performed showing a total occlusion of the left external iliac artery and some smaller contrast defects in other vessels (Fig 1)

The patient was referred to the Thoracic Surgical Clinic on the evening of July 26 for further treatment On admis sion she still complained of pain in both legs The mus cular cramps were less pronounced The left leg was pale and cold below the middle of the thigh and she was not able to move the lower leg The right foot was also some what cold but no severe circulatory disturbance was present on that side Chest X ray and ECG were normal

An acute embolectomy was immediately performed and through an incision in the left femoral artery large amounts of red yellowish thrombus could be extracted both proximally and peripherally with the aid of a Fogarty catheter The specimen was sent for microscopic investi gation After completion of the embolectomy a blood flow of 300 ml/min was measured in the femoral artery and the foot immediately became red and warm

Some hours after operation the left leg started to swell due to a diffuse oedema in the previously ischaemic mus culature Eight hours after the embolectomy the lower leg was so intensively swollen that the venous circulation be gan to be compromised To prevent further deterioration of the circulation and in order to decompress the calf muscles that were in immediate danger of pressure ne croses a fasciotomy operation had to be performed The oedematous muscles literally bulged out through the in cision leaving a 15 cm diastasis between the skin edges

In the meantime the right foot had begun to be isch aemic and an attempt was made to perform an embolecto- my on the right leg Even though the embolectomy cathe ter could be passed all the way down to the foot no



Fig 1 Angiogram showing complete occlusion of left external iliac artery

embolic material could be retrieved A new arteriography was therefore performed on the right leg and showed a subtotal occlusion of the popliteal artery immediately above the knee A repeat embolectomy this time through the right popliteal artery was performed and an embolus that was partly attached to the vessel wall could be extracted with the aid of a Fogarty catheter In addition some fresh thrombotic material could be removed from the distal arteries of the leg The right foot immediately became warm and distant pulses could be palpated Follow the operation however the same thing happened as the left side namely the right lower leg became so len due to the postischaemic oedema that a fasciomy procedure had to be carried out on this side as well

At this stage the general condition of the patient was markedly affected Due to renal damage by myoglobin precipitation and to the repeated operations and blood transfusions the kidneys started to fail Serum creatinine wa above 600 mmol/l Fluid accumulated in the lungs but the condition could be controlled with intermittent respirator treatment and large doses of furosemide

The result of the microscopic examination of the emboli was available on the sixth day after the first embolectomy A strong suspicion of cells originating from a cardiac myxoma was at hand This finding motivated an angiocardiographic examination of the heart A pulmonary angiogram was performed and a 4×6 cm large contrast defect was seen in the left atrium suggesting the presence of a pedunculated myxoma On the night after the investigation the patient experienced a sudden thrust of pain in the right hypocondrium suggesting an embolus to the liver It was decided not to wait with removal of the myxoma

On the next day Aug 4 the operation was performed through a median sternotomy and with the aid of extra corporeal circulation and temporary cardiac arrest The friable myxoma together with its attachment on the base of the interatrial septum could be removed (in one piece) without problems (Fig 2) Except for postopera[…]ing which necessitated re-operation the pos[…] course was uneventful and the patient made a […] rapid recovery The kidney function returned to […] within a week

Rehabilitation was for natural reasons hampered […] large open wounds on both lower legs A skin tra[…]tion was suggested by the plastic surgeons but […] postponed due to a wound infection The swe[…] calf muscles had in the meantime diminished […] week s daily application of wound tape the inc[…] the fasciotomy could be closed by direct suture […] sides leaving a very satisfactory cosmetic result […] active mobilization program could now be sta[…] after about a month the patient was able to walk […] a follow up examination in Jan 1977 she could […] out problems and had resumed work The le[…] slightly slimmer than the right and some reduction […]cular strength was evident Circulation was […] both legs

COMMENTS

Peripheral arterial embolism in a previously young individual is a rare occurrence A[…]ditions reported to cause arterial emboli […] people may be mentioned bacterial endo[…] mitral valve disease with atrial fibrillation […]tain uncommon coagulation disorders […] these conditions could be demonstrated […]tient She had no history of fever, cardiac […] or coagulation problems The heart was […] auscultation ECG and chest X ray The d[…]



Fig 2 The removed myxoma with its attachment […] interatrial septum

osis was obtained through microscopic ex tion of the embolic material from the legs the massive nature of the embolization was sed atrial myxoma was considered a possi although her age and the absence of cardiac oms spoke against this diagnosis

initial clinical picture with bilateral severe amps was most confusing The pronounced ilar cramps can be explained by the fact that nbolization took place during exercise (swim and that the response of the musculature to n ischaemia is probably different during exer nd at rest The electrolyte disturbance that t hand on admission may also have contrib o the altered reaction The gradual deteriora f the arterial circulation is explained by sec y thrombosis distal to the emboli The mus ischaemia became finally so pronounced as ise release of myoglobin and enzymes Ap nately 40% of patients with left atrial myx have peripheral embolization of tumour frag (4) Almost all organs have been reported to site of emboli (9 17) Cerebral emboli are nt and fatal outcome has been reported (3) st patients with left atrial myxoma have car ymptoms due to obstruction of the mitral ori

myxoma usually originates from the lower f the interatrial septum and is pedunculated the myxoma has reached a certain size it will ect the mitral valve during diastole and will in ay simulate mitral stenosis (6) Frequently nour is not detected until an operation for a ted mitral stenosis is undertaken (11 13) tutional symptoms such as fever malaise loss and high ESR are reported to occur in 90% of the cases but these findings are un c and difficult to interpret (5)

ocardiography is of great value in the diagno cardiac myxoma At the time in question this ostic aid was not available at our institutions uld also be born in mind that cases have been ed in which the myxoma has been small and d in the left ventricle and might thus have overlooked at an echocardiographic examina ocused on the atria (1) Therefore an angio ic examination is usually necessary and the t way is to perform a pulmonary angiogram the myxoma will appear as a mobile contrast when the contrast medium has reached the num

our patient the postischaemic oedema was so severe that a bilateral fasciotomy had to be performed Had this not been done further muscular damage would probably have taken place Fortunately the muscular swelling soon diminished rendering skin transplantation unnecessary and an excellent cosmetic result was obtained after direct wound closure The patient is now back in her previous occupation as a swimming teacher and has only a slight reduction of the muscular strength in her left leg

Atrial myxoma is generally considered to be a benign tumour although the tendency to obstruct the mitral valve and to embolize makes it clinically malign Recurrence is very rare and is probably due to incomplete removal of the tumour (16) Follow up examination including echocardiography is however warranted

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Acta Med Scand 206 127–129 1979

Diastolic Wave Initiating Ventricular Tachyarrhythmias and Suppressible by Lignocaine and Isoprenaline

Erik Orinius

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ACT A patient is described with ventricular ...rdia and premature beats (VPB) probably in ... by a diastolic wave, which—like the VPBs— ...e eliminated by lignocaine and isoprenaline

ds ventricular tachycardia prolonged Q-T inter ...ave alternans

...d Scand 206 127 1979

...ed Q-T interval and alternating T waves are ...ted with paroxysmal ventricular tachycardia ...nd ventricular fibrillation (VF) but the ar...ias are not so frequent that the mere finding ...olonged Q-T interval or alternating T waves ...s acute VT/VF prophylaxis A more ... warning sign has been described in patients ...rolonged Q-T interval during quinidine ...nt (1) It is a diastolic wave that cannot be ... or U in a strict sense It nearly always ends ... ventricular premature beat (VPB) and such ...receded VT/VF by minutes–hours in 9 of ...ents in that series Another 23 of those ...ie treated patients had prolonged Q-T in... without developing VT/VF and none of ...howed the diastolic wave

...report concerns a patient without quinidine ...nt who demonstrates that the diastolic wave ... following VPB could be eliminated by lig... and isoprenaline while the Q-T interval ...ed prolonged

CASE REPORT

...ar-old girl was admitted acutely for a preoperative ...investigation during treatment of septicemia She ...ind to have a severe aortic incompetence and an ...m of the right sinus Valsalva with rupture into the ...ntricle ECG was normal

...days before the planned surgery digoxin intoxica...is suspected and the medication was discontinued The serum concentration of digoxin analyzed on the next day was 3 3 nmol/l (therapeutic range 1 0-2 5) However before that was known the patient developed an observed circulatory arrest ECG recorded after some minutes of resuscitation measures showed asystole The circulation could be restored but the patient had not regained consciousness when an acute operation was started A Bjork-Shiley valve prosthesis was inserted in aortic position and a small fistula from the right sinus of Valsalva to the right ventricle was closed The procedure was uneventful

On the next morning the patient was still unconscious ECG did not show any Q–T prolongation and the patient was normokalemic Some hours later—23 hours after the circulatory arrest—she developed a long VT which disappeared during external cardial massage given because of low blood pressure

The VT was of torsade de pointe type (Fig 1) The patient had not been treated with quinidine or any similar drug nor had any phenothiazine or derivatives been given

When lignocaine treatment was started following the VT the patient had VPBs in bigeminy or quadrigeminy which were preceded—most easily seen in lead III—by a remarkable T–Q wave appearing in a 2 1 or 4 1 pattern (Fig 2) After 75 mg lignocaine i v both the diastolic waves and the VPBs disappeared leaving the prolonged Q–T interval (Fig 3)

When the lignocaine infusion rate was reduced on trial the diastolic wave returned in a 2 1 pattern and as the dose was further reduced even the VPBs reappeared in bigeminy As the lignocaine dose was again increased both the diastolic waves and the VPBs disappeared

Lignocaine treatment was discontinued after 8 hours Five hours later premature beats with aberrant ventricular conduction but normal QRS width appeared and as before they were preceded by a T–Q wave in a 2 1 pattern (Fig 4) This time isoprenaline was given (0 5 μg/min) and both the diastolic waves and the VPBs disappeared (Fig 5) The antiarrhythmic therapy was stopped about 12 hours later i e 48 hours after the circulatory arrest No more episodes of VPBs or VT occurred

The patient made a complete physical and psychic recovery

Abbreviations VT = ventricular tachycardia VF = ventricular fibrillation VPB = ventricular premature beat

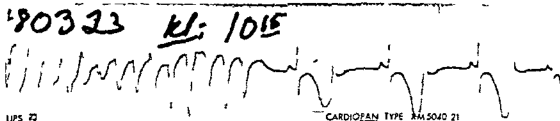


Fig 1 VT of torsade de pointe type 220/min followed by sinus rhythm with ventricular ectopic beats in bigeminy Rhythm monitoring lead paper speed sec

COMMENTS

The ECGs in Figs 2 and 4 show Q–T prolongation alternating T waves and premature beats Ventricular tachyarrhythmias are well known complications of prolonged Q–T interval (9) and in alternating T waves 4 out of 13 cases had also had VF (6) Closer examination of the ECG in Fig 4 reveals most clearly in lead III that the T wave after inscribing its vertex does not proceed downwards but turns into a wave (↑) with greater amplitude than that of the T wave It is slightly greater even if one subtracts the amplitude of the overlapping P wave so this cannot be called an U wave in a strict sense (5)

That this diastolic wave does not only precede but also initiates the VPBs is probable from Fig 2 The wave is easily seen in lead III (↑) before each of the two VPBs (What looks like a P wave just preceding the VPB is instead the last part of the diastolic wave and the first part of the VPB) In contrast to QRS complex no 5 no 4 is preceded by a deeply negative T wave in leads I and II as are the VPBs but the T wave preceding QRS no 4 is not followed by the marked positive wave in lead III (the absence marked ↓) Therefore the c wave probably intiates the VPBs

The ECG in Fig 3 demonstrates that lig could eliminate the diastolic waves and the well as the T wave alternans Ejvinsson (l study whether lignocaine could eliminate stolic waves and the following VPBs b it effective in preventing VT/VF during treatment

Whether the premature beats in ECG ventricular or supraventricular cannot be without fusion beats premature P waves QRS duration is somewhat difficult to me is probably not more than 0 09 sec E premature beats do look rather like the plexes in lead II they differ strikingly These premature beats might thus be of origin

ECG no 5 demonstrates that both th waves and the premature beats disappear isoprenaline infusion Isoprenaline has to abolish primary T wave abnormalities contrast to epinephrine—not to trigger V tient with familial long Q–T syndrome and ble brain damage after a prolonged attack culatory arrest (2)

The practical consequence of this is th preceded by diastolic waves can be treated

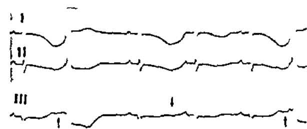


Fig 2 Sinus rhythm with VPBs preceded by a T–Q wave seen most easily in lead III (↑) In contrast to QRS complex no 5 no 4 is preceded by a deeply inverted T wave in leads I and II as are the VPBs but the T wave preceding QRS no 4 is not followed by a marked positive wave in lead III (↓) Extremity leads I II III Paper speed 50 mm/sec

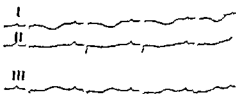
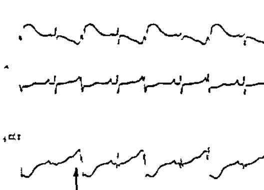
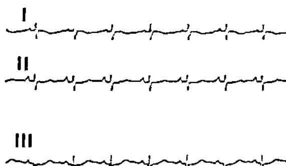


Fig 3 The same leads as in Fig 2 about 18 during lignocaine treatment The T–Q wa VPBs have disappeared Paper speed 50 mm/se





... inus rhythm with ectopic beats in bigeminy. When ... ave of a sinus beat has inscribed its vertex—most ... en in lead III—it does not proceed downwards but ... o a T–Q wave (↑) with greater amplitude than that ... wave. It is slightly greater even if one subtracts ... litude of the overlapping P wave and so it is not an ... Extremity leads I, II, III. Paper speed 25 mm/...

Fig. 5. The same leads as in Fig. 4 following 20 min o... isoprenaline therapy. The T–Q wave and the ectopic beats have disappeared. Paper speed 25 mm/sec.

...id that this probably should be done as a ...laxis against VT/VF. Lignocaine is probably ...st drug.

... can only speculate about the genesis of the ...c waves and the ventricular tachyarrhyth... ...nd how lignocaine and isoprenaline affect ... ome ECGs reproduced in articles about long ...ndrome and alternating T waves show the ...c wave (6, 7), but the present patient did not ...ly previous history corresponding to those ...nes. Nor had she been treated with quini... ...henothiazine or derivatives. In Ejvinsson's ...1) all patients were or had been on digoxin ... me days before the start of quinidine treat... ...nd the appearance of VT/VF, and it might be ... basis of quinidine syncope is digitalis. The ... patient was treated with digoxin to a slightly ...erum concentration, and this might have ...uted to the tachyarrhythmias. The patient ...mptoms of brain damage during a week or so ...ng the circulatory arrest prior to surgery, and ...erebral disorders have been described to be ...ated with deeply inverted widened T waves ...ominent U waves but not ventricular tachy... ...ımias (4). However, *if* the brain is the tissue ...where digitalis induces ventricular tachyar... ...ıas, the anoxic damage might have released ...echanism in the present case.

Recently, monophasic action potentials in patients with long Q–T syndrome have been shown to have an intermittent second deflection (3). This deflection may constitute the diastolic wave in the surface ECG of the present patient.

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Acta Med Scand 206 131–135 1979

Myasthenia Gravis and Werlhof's Disease

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RACT A case of Werlhof's disease (immune ibocytopenia) associated with myasthenia gravis cribed The two disorders developed within a ionths of each other The immunological and ical aspects of the association are discussed

words myasthenia gravis thrombocytopenia of's disease

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rlhof's disease thrombocytopenia has been i to be due to accelerated destruction of ets by an immune mechanism (9) Several of the disease are recognized e g idiopathic bocytopenia (ITP) when no exogenous factor parent and drug induced or symptomatic bocytopenia in the course of certain other lers (2) A humoral mechanism is considered isible for platelet destruction A cell mediated inism has not been demonstrated convincing

isthenia gravis (MG) is a disorder of muscular transmission which is probably due autoimmune attack reducing the available choline receptors of the postsynaptic mem s of skeletal muscle This reduction has been nstrated biochemically and histologically and to have a direct relation with the circulating odies reacting with acetylcholine receptor in (4) Immune complexes at the motor end i (MEP) have been demonstrated (5) Thymic malities are observed as thymomas in 10–15% patients and follicular hyperplasia in 50–60% e thymuses removed by operation An au ative review is given by Drachman (4)

e association between MG and other auto ine diseases has been reported frequently ugh epidemiologic studies are scarce At least natoid arthritis (12) and thyroid disorders (16) are more common in myasthenic women than can be expected Pure red cell aplasia has some prefer ence for myasthenic patients because of its associa tion with a thymoma (11)

A number of associations of Werlhof's disease and other autoimmune disorders have been de scribed Immune thrombocytopenia may occur in the course of systemic lupus erythematosus (2) or in association with autoimmune hemolytic anemia (Evans syndrome) (2) An association with Ha shimoto s disease has been described (3) Three cases of MG associated with ITP have been re ported recently (14 15 19) In these cases the dis orders did not arise simultaneously MG developed many years after the ITP (14 19) or the reverse (15)

The present paper reports on a case of MG and Werlhof s disease occurring at about the same time

CASE REPORT

A 19-year-old man was in good health until Feb 1976 when he noticed a stiffness in his face and a strange way of laughing In May 1976 swallowing and articulation be came difficult and he experienced diplopia Proximal weakness in arms and legs supervened His symptoms increased after exercise and were more prominent at night

The diagnosis of MG was made after a positive edro phonium chloride test and was confirmed by typical decremental response of the muscle action potentials after supramaximal stimulation of the nerve at a rate of 3 per second Treatment with prostigmine bromide and pyridostigmine bromide was started in June and am benonium chloride was added in August Nevertheless his symptoms increased and he was brought to our hospi

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Abbreviations ITP = idiopathic thrombocytopenia MG = myasthenia gravis MEP = motor endplates

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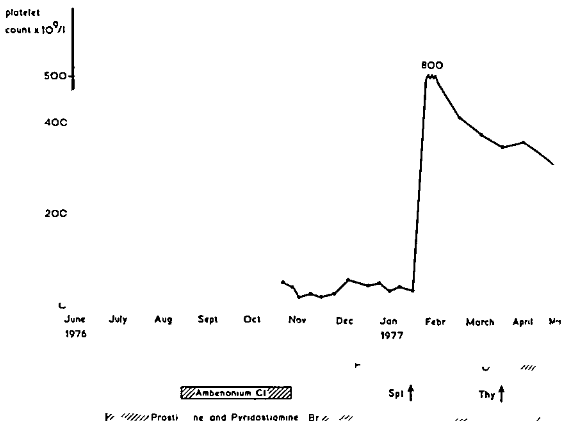


Fig 1 Clinical course *P*=prednisone (60=60 mg daily 60/0=60 mg on alternate days) *Spl*=splenectomy *Thy*=thymectomy

in Oct 1976 because of attacks of respiratory insuffi

On admission he was in general good health with the typical picture of a generalized MG His vital capacity at rest was reduced to 80% of the normal value A chest X ray revealed no evidence of a thymoma and antimuscle antibodies were not detected Thymectomy seemed indi cated Thrombocytopenia was detected at the routine laboratory examinations There was no history of purpura or other bleeding manifestations The family history was un remarkable and no bleeding disorders myasthenia or thyroid diseases were known The spleen was not palpa ble and no lymphadenopathy goitre or bleeding manifes tations were found

The platelet count in an electronic particle counter confirmed by phase contrast microscopy ranged from 46 000 to 55 000/mm³ WBC was 7 800/mm³ with a normal differential count Serum electrophoresis and tests for re nal hepatic functions revealed normal findings Cultures of urine and sputum were negative

Examination of a bone marrow smear revealed an in creased number of megakaryocytes with a normal appear ance Survival of ⁵¹chromium labelled donor plateles was markedly shortened to 72 hours Coagulation tests yielded normal results serum thyroxine level was within the nor mal range 8 7 μg/100 ml Tests for rheumatoid factor antinuclear and antithyroid antibodies gave n sults The patient s blood group was B Rhesus HLA typing A_2 A_3 B_3 B_7 Cytotoxic a antibodies were not found The complement C_3 normal

The diagnosis of Werlhof's disease thrombocytopenia) was made None of the dr the patient have been reported to provoke a thrombocytopenia

Ambenonium chloride—the only drug tha added recently—was withheld In the next th the platelet count did not increase and ranged to 40 000/mm³ Subsequently treatment with p in a dose increasing from 30 to 60 mg daily wa the next six weeks the platelet count rose some did not exceed 65 000/mm³ The bleeding time 7–9 min The myasthenia improved only parti nisone treatment was continued on an alter dose scheme Splenectomy was considered thymectomy was contraindicated by the thrombocytopenia

Splenectomy was performed in Jan 1977 fo lowed by a prompt and sustained remission of the platelet count remained above 300 000/mm³ Th was performed two months later Following ind tions a short period of ventilatory assistance wa

I *Immunological data on the patient*

of disease	Thrombocytopenia	Remission of thrombocytopenia	
		1 week	*6 months*
nent	Untreated	Prednisone splenectomy	Thymectomy
atelet antibodies	–	–	–
atelet antibodies	+		+
t bound IgM	Weak	–	–
t bound IgG	++	+	–
tibodies to skeletal muscle	– (1 10)	–	+ (1 4) – (1 10)
tibodies to MEP	Dubious		+

listological examination of the spleen revealed no ialities A few germinal follicles were found in the and there was no thymoma Following the tomy the myasthenic symptoms decreased and dnisone dosage could be reduced gradually but not be discontinued The clinical course is sum d in Fig 1 A recent respiratory tract infection was d by a short exacerbation of the myasthenia nmune thrombocytopenia remained in remission nout

unological studies were performed on several occa i the course of the disease

bodies to skeletal muscle were detected by an indi nmunofluorescence technique described by Felt t al (7) Only fluorescent anti IgG sera were used *bodies to MEP were detected by an indirect im* uorescence technique using fluorescent anti IgG as recently described by Sontag Tschroots et al

let bound immunoglobulins were detected by di munofluorescence on gel filtered platelets as previ escribed (17)

let antibodies were detected in sera by an indirect ofluorescence technique previously described (18) serum and platelet rich plasma prepared from anticoagulated blood were incubated washed by ation and stained with fluorescent rabbit antihuman d IgM

results of the immunological studies are given in I

control study no platelet antibodies were found in *ra of 12 patients* with active MG and no skeletal antibodies were detected in the sera of 12 patients Verlhof's disease

DISCUSSION

issociation of MG and ITP has been reported ee cases in the past two years Segal and traub (19) described a patient with ITP who i remission after splenectomy and developed Hashimoto s disease and MG ten years later Pinals et al (14) described a patient with Graves disease followed by ITP and 12 years later by MG Remuzzi et al (15) described a patient with MG who de veloped ITP ten years later All these patients were females Platelet antibodies were found in the first case by a platelet factor 3 release assay and in the last case by a serotonin release test The antibodies were not characterized HLA typing did not show a definite association between HLA type and disease HLA B_1 was found in the former two cases and HLA B_8 in the latter case

MG has a prevalence of 2 4 and 8 6 per 100000 respectively for men and women (10) The preva lence of Werlhof's disease is not exactly known but is estimated from clinical admission data to be about 4 per 100000 The female male ratio in Werlhof's disease is about 3 1 Thus the chance of coincidence of MG and Werlhof's disease is ex tremely small especially with respect to males In a series of 400 consecutive patients with MG ob- served by one of us (H J O) only one patient was seen who probably had suffered from Werlhof's dis ease in the past a young woman suffering from MG from the age of 27 who underwent splenectomy at the age of 22

Our present patient is a young man who de veloped MG and ITP within a few months of each other The thrombocytopenia was discovered on a routine examination after intake of anticholin ergic drugs for several months Withdrawal of ambenonium chloride did not change the platelet count notably the other drugs could not be with held without endangering the patient but they are not known to have elicited an immune

thrombocytopenia Remission of the ITP was not achieved on prednisone treatment but splenectomy was followed by a persistently normal platelet count

On admission IgG platelet antibodies were found in the patient s serum and IgG as well as small quantities of IgM on his platelets The serum antibodies persisted throughout the course but the platelet IgM disappeared in a few weeks the IgG several weeks later when remission was reached The rapidly disappearing IgM is consistent with the recent onset of immune thrombocytopenia After splenectomy IgG antibodies were still present in the serum Because a platelet transfusion had been given for survival studies, the presence of isoantibodies at that time cannot be ruled out Platelet bound antibodies were not detected six months after splenectomy

IgG antibodies to skeletal muscle were not found initially when a 1 10 diluted serum was tested They were detected however when a dilution of 1 4 was used Thus they were found in a very low titer IgG antibodies to MEP were detected most clearly in a later phase of the disease when thymectomy had been performed and the patient was still on prednisone IgG antibodies to skeletal muscle are found in 22% (7) and antibodies to acetylcholine receptor substance in 87% (4) of MG cases

Serum platelet antibodies belonging to the IgG s are found in about 60–70% of patients with P (9) Platelet antibodies were not found in the sera of our 12 control patients with MG and skeletal muscle antibodies were not detected in 12 control patients with Werlhof's disease Platelet antibodies are supposed to be produced largely in the spleen but also in other parts of the reticuloendothelial system (9) Production of acetylcholine receptor antibodies by thymic lymphocytes has been reported recently (22) In our patient antibodies to MEP were however still present after thymectomy Whether the platelet and MEP IgG antibodies are cross reacting or independent cannot be determined from our data

A modest association between MG and HLA B_8 has been described by several authors (7) Goebel et al (8) reported an association between ITP and HLA B_8 and HLA B_{12} In a recent study we could however not find associations of any significance (21) Neither B_8 nor B_{12} are present in the patient presented here

The practical consequence of the assoc autoimmune disorders is to carefully search others when one of them has been found is especially important when an operation splenectomy thymectomy or thyroidectomy sidered Serious complications—such as b due to thrombocytopenia respiratory insuff in myasthenia or thyrotoxic crises—may b vented by adequate preoperative treatment

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Effects on Muscle Electrolytes of Potassium and Magnesium Infusions, Spironolactone Medication and Operation in a Case of Primary Aldosteronism

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RACT Serum and muscle electrolytes were uned in a case of primary aldosteronism before ter potassium and magnesium infusions as well onolactone treatment and following surgery ed potassium infusions resulted in a transient lization of the muscle potassium (K/m) fol within 3–4 days by a return to the previously 'm Magnesium infusions did not give any in in muscle magnesium (Mg/m) On the con there was a decrease in Mg/m concomitant a decrease in K/m Treatment with spiro- ne for one month was followed by a nor- tion of both serum and muscle electrolytes ing surgery the serum potassium and K/m re- l normal, but the serum magnesium (Mg/s) g/m showed a decrease to subnormal values the initial findings of normal Mg/s and Mg/m as excretion of more than 80% of the i v ium dose this may indicate that there was a ium deficiency in the skeletal pool

rds aldosteronism spironolactone intra-extra electrolytes

:d Scand 206 137 1979

es of muscle tissue *in some patients with* / hyperaldosteronism have shown a de l content of potassium and an increased con- sodium (5–8 15) Magnesium has not to our dge been analysed in muscle tissue in this : The serum level of magnesium has been :d variously as high normal or low in pri hyperaldosteronism According to Dupas- 11) however the serum level is normal in 6 8 patients Hanna and MacIntyre (13) in ted the effect of aldosterone injections on l and adrenalectomized rats and found no in muscle magnesium in the normal group lecrease in the adrenalectomized group have studied muscle potassium and muscle magnesium in a case of primary hyperaldosteronism before and after potassium and magnesium infusions We have also studied the effects of treatment with an aldosterone antagonist spironolactone (Aldactone®) on the muscle electrolytes

METHODS

Muscle biopsies were obtained ad modum Bergstrom (2) from the lateral portion of the quadriceps femoris muscle after an overnight fast The biopsies (40–80 mg wet weight) were weighed repeatedly on an electrobalance after carefully dissecting them free form visible connective tissue and fat. The wet weight was obtained by extrapolation to zero time The dry weight was obtained after drying to constant weight in an oven Fat was extracted with redistilled petroleum ether The muscle pieces were wet ashed in 1N nitric acid and the contents of sodium potassium and magnesium were determined by atomic absorption spectrophotometry Chloride was determined indirectly after precipitation with silver nitrate The silver residues were determined by atomic absorption spectrophotometry The intracellular electrolytes were calculated according to the chloride method (12) assuming chloride is freely diffusible across the cell membrane A normal resting membrane potential (4) was used to calculate the chloride equilibrium over the cell membrane The serum and muscle electrolytes are presented in Table I

CASE REPORT AND RESULTS

The patient was a 55-year-old woman who had difficulties in concentrating and was investigated at a psychiatric clinic in 1967 Arterial hypertension was found and the patient was treated with various diuretics and later with β-blocking agents without success She had a tendency to a low serum potassium level despite a high potassium supplementation She often had headaches in the occipital region mostly in the morning During the last two years

Abbreviations m=muscle s=serum ec extracellular ic=intracellular

Table I *Serum and muscle electrolytes*

FFDS = fat free dry solid

Biopsy no	Serum (mmol/l)		Muscle (g/100 g FFDS)			Muscle (mmol/100 g FFDS)		
	K	Mg	H_2O/m	H_2O/ec	H_2O/ic	Cl/m	Na/m	K/m
I	2 2	0 78	385	72 4	313	9 06	23 4	38 2
II	3 0	0 81	363	85 8	277	10 8	17 5	40 6
III	2 8	1 29	447	219	229	26 3	32 8	34 0
IV	3 9	0 80	378	80 2	298	10 8	14.5	44 8
V	3 5	1 07	379	167	212	20 2	25 1	33 3
VI	4 2	0 90	381	105	276	14 0	19 4	45 4
VII	4 6	0 67	423	138	285	19 5	19 6	44 [illegible]
Normal values	3 6–5 4	0 80–1 00	305–384	<120	231–315	<14 0	<19 0	40 8–[illegible]

she also complained of vertigo and chest pains on heavy exertion She had also observed a successively increasing muscular weakness

In 1976 she visited the emergency ward because of a painful shoulder A blood pressure of 260/125 mmHg was registered On admission she had a very low serum potassium (K/s) (2 2 mmol/l) normal serum sodium (Na/s) (141 mmol/l) slightly low serum magnesium (Mg/s) (0 78 mmol/l) and a high total carbonate (31 mmol/l) A renal X ray showed no abnormalities The urinary excretion of aldosterone was clearly above normal and the renin values were extremely low

A muscle biopsy (I) was performed on admission and showed a low muscle potassium (K/m) content and a high muscle sodium (Na/m) content The muscle magnesium content (Mg/m) was normal The intracellular concentration of sodium (Na/ic) was high and that of potassium (K/ic) very low The patient was given 500 mmol potassium chloride by vein but the K/s was still below normal 3 0 mmol/l A second muscle biopsy (II) showed that K/m had increased to nearly normal and K/ic to normal and Na/m had decreased

Two days later after infusion of 30 mmol magnesium sulphate and only oral potassium supplementation a third *muscle biopsy (III) was performed The analyses showed* a rapid retreat to the original low K/m and high Na/m values Mg/m however decreased In the interval between biopsies II and III the patient had excreted more than 300 mmol potassium in urine

She was again given i v potassium supplementation this time till a normal K/s was obtained A new muscle biopsy (IV) again showed that the K/m values increased this time to normal values for both K/m and K/ic Four days afterwards following an infusion of 30 mmol *magnesium sulphate and only oral potassium supplementation* a new muscle biopsy (V) showed a repetition of the retreat to pretreatment values and a decrease in Mg/m During these four days she had excreted about 1000 mmol potassium in urine In the 24 hours following the magnesium infusion 26 mmol magnesium was excreted in the urine

Thereafter the patient was treated with spironolactone (Aldactone®) 25 mg×4 by mouth for one month The serum electrolyte values following this treatment showed a normalization of all electrolytes including [illegible] bonate and K/m increased to normal values [illegible] and K/ic (VI) Two months later the patient was [illegible] upon and a cortical glomerulosa adenoma of [illegible] was excised

Two months after the operation during which [illegible] patient was off medication a last muscle biopsy [illegible] formed (VII) All serum electrolyte values [illegible] mal and about the same as after spironolacto[illegible] ment except for magnesium which had decrease[illegible] normal levels K/m and Na/m had also nor[illegible] Mg/m had decreased

DISCUSSION

Our studies confirm the earlier findings of [illegible] K/m and K/ic and increased Na/m and [illegible] primary hyperaldosteronism (5–8 15) [illegible] normal which speaks against a musc[illegible] nesium deficiency It is quite obvious [illegible] ferred case that administration of large [illegible] of i v potassium resulted in a rapid [illegible] through the kidneys The potassium su[illegible] tion gave only a transient increase in K[illegible] for one or two days

Spironolactone is a well known and [illegible] hibitor of aldosterone and has been sh[illegible] normalize the K/s level in cases with [illegible] aldosterone production (9) This proved [illegible] in our patient who showed a return to nor[illegible] and Mg/m Thus spironolactone seems to [illegible] in the treatment of hyperaldosteronism [illegible] diseases nephrosis and congestive heart [illegible] often accompanied by a secondary aldost[illegible] which may be further accentuated by the thiazides and frusemide (10 14) this may [illegible] more liberal use of spironolactone in the [illegible] of these diseases

	ol/kg H_2O/ic)	
	K/ic	Mg/ic
	122	14 3
	146	15 2
	146	16 8
	149	13 4
	154	14 4
	163	14 5
	153	12 9
	143–191	*12 4–17 8*

potassium infusion, both K/m and K/ic in . This was confirmed in a repeated trial is points to a normal Mg/m content as it is wn that *magnesium stimulates the Na K* which is needed to promote the ingress of n into the cell

magnesium infusion the urinary potassium was high and K/m decreased greatly as potassium was administered Mg/m a paradoxical decrease The same hap fter a repeated magnesium infusion A rrelation between K/m and Mg/m has been rated earlier (1) and may perhaps help to he paradoxical decrease in Mg/m Another on may be the primary aldosteronism per s been shown (3) that when potassium is this disease *there may be an increase in* ne secretion and an increased loss of n in the urine Concomitantly there may an increased urinary loss of magnesium /m decreases the intracellular water de n parallel Thus the cell seems to try to c constant

magnesium infusion 90% of the infused Mg reted in the urine during the first 24 hours en found (16) that an excretion of less than licates magnesium deficiency while more % contradicts deficiency Again the finding atient of an excretion of 90% of the given is in favour of a normal body magnesium

lood pressure returned to normal after op without any further medication The extra acellular electrolytes normalized except for d Mg/m which both showed low values h urinary magnesium excretion as de scribed in primary aldosteronism (11) together with a normal Mg/m may be explained if Mg is lost from the skeleton during aldosterone hypersecretion In that case the skeleton should try to attract magnesium after operation to compensate for the earlier losses *The low values of Mg/s and Mg/m* found in our patient after operation are in ac cordance with such a theory

ACKNOWLEDGEMENT

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The Syndrome of Inappropriate Secretion of Antidiuretic Hormone

A Case Report

Erik Hagg Folke Lithner Bengt Lindqvist and Frej Fyhrquist

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ACT A 72 year-old woman with the syn of inappropriate secretion of antidiuretic e of unknown cause during more than one observation is reported Plasma vasopressin re excessively elevated, even during a water t Her serum electrolyte abnormalities and state were ameliorated after fluid restriction treatment with demeclocycline the patient to increase fluid intake without deteriora

ls vasopressin hyponatremia demeclocycline
l Scand 206 141 1979

idrome of inappropriate secretion of an - hormone (SIADH) is characterized by wa ition hyponatremia low serum osmolality esence of urinary osmolality which is less timally dilute and continued renal excretion n (1) The syndrome has been described in on with a variety of diseases, the most being malignancy (most often lung car disorders of the central nervous system monary diseases (?) In addition certain g chlorpropamide and carbamazepine se SIADH (4)

scribe a woman who presented the features)H but in whom we have hitherto been to reveal an underlying cause Measure f plasma ADH after a water load showed h levels In addition the result of short atment with demeclocycline is reported

CASE REPORT

in aged 72 who since 1958 has had allergic na and bronchial asthma She has been treated inchodilators and expectorants and since 1960 iacort® (triamcinolone) 4 mg daily For as long as emember she has had a tendency to thirst with frequent intake of water She has never had any skull trauma or meningoencephalitis On July 7 1977 she fell acutely ill with fever (about 38–39°C) malaise frequent urination and mental confusion

On admission to the local hospital five days later she was still confused No edema or signs of dehydration were noted Temperature was 39 3 C and BP 150/80 mmHg There were no pareses The tendon reflexes were difficult to elicit but without assymmetry There was a mild neck rigidity but Lasègue s sign was negative ESR blood Hb level leukocyte count serum bilirubin GOT and GPT levels were normal On the day of admission serum sodium was 115 mmol/l chloride 79 mmol/l and creatinine 70 μmol/l Serum potassium was initially 3 8 mmol/l but tended later to be low (minimum value 2 2 mmol/l) as did serum calcium (minimum value 1 8 mmol/l) Repeated blood cultures were negative A urinary culture showed significant bacteriuria the sediment containing increased amounts of erythrocytes and leukocytes A diagnosis of acute cystopyelitis was made and the patient received antibiotics The fever decreased after one week a low grade fever persisting for another two months

Because of the severe serum electrolyte abnormalities the patient was also treated with sodium chloride 3–7 5 g daily together with glucocorticoids and fluorhydrocortisone Serum sodium and chloride increased but remained subnormal serum sodium levels were most of the time below 130 mmol/l and chloride below 90 mmol/l Potassium chloride and calcium gluconate lactate were also administered Daily urinary output varied between 1 and 3 8 l Urinary excretion of sodium was 171–444 mmol/24 h and of potassium 26–167 mmol/24 h

After four weeks in the local hospital she was referred to the Department of Internal Medicine Umeå University Hospital where she was treated on four occasions during the period Aug 1977–Oct 1978

On the first admission the patient was bed ridden and disorientated There was a generalized muscular wasting but the results of the neurological examination were normal Eye ground examination revealed no papilledema ECG showed a sinus tachycardia and Q waves in I aVL and V_{4-7} A bronchoscopy was normal as were repeated

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Abbreviations ADH = antidiuretic hormone SIADH = syndrome of inappropriate secretion of ADH

Table I *Result of water loading test*

Time (h)	Serum osmolality (mosmol/kg)	Urine osmolality (mosmol/kg)	Serum sodium (mmol/l)	Plasma vasopressin (pg/ml)
0	245	412	129	39 6
08	255	481	127	36 3
10	265		129	31 7
12	270	481	127	64 5
14		750 ml of water ingested		
14 30	260			42 9
16	265	304	124	44 6
18	275	233	124	56 1

chest X rays (the last one performed in Oct 1978) and an i v pyelography Renal arteriography did not reveal any abnormalities of the kidneys A liver scan was normal X ray examination of the pituitary fossa and EMI scanning of the brain were normal except for a moderate bilateral widening of fissura Sylvii Echoencephalography showed a slightly increased width of the third ventricle EEG—initially pathological with a pronounced episodic bilateral synchronous abnormality probably projected from subcortical structures—was quite normal in April 1978 EMG of the upper and lower limbs was normal Repeated lumbar punctures (Aug 29 Sept 7 and 27 Oct 28 Dec 8 1977 and Jan 4 1978) were normal except for an elevated protein content which eventually decreased to normality 1010 1090 765 525 511 398 mg/l Spinal fluid electrophoresis initially showed a slight oligoclonal increase of IgG which later disappeared Blood WR was negative Serum and urinary electrolyte values were unchanged Urinary concentration ability during thirst was 775 mosmol/kg and did not increase after intranasal administration of 20 μg of the synthetic vasopressin analogue desmopressin (Minirin®) There was no glucosuria Urinary porphobilinogen was normal

When suspicions of SIADH were raised glucocorticoids and fluorhydrocortisone were omitted and the daily fluid intake was reduced to 0 5–1 l In four days serum sodium levels had increased from about 120 to 130 mmol/l and serum chloride levels from about 90 to 97 mmol/l and thereafter most of the serum values for sodium were 130–135 and for chloride 94–104 mmol/l In addition serum potassium and calcium rose to normal levels A few days after fluid restriction had been initiated the patient s mental condition improved and she could sit in a chair After three weeks her mental state was entirely restored and she began to walk

Water load test and plasma ADH measurements

A water load test was performed on Oct 12 1977 During the test no food or fluid was given after midnight At 2 p m the patient ingested 750 ml of water during 15 min Specimens were taken for plasma ADH serum and urine osmolality and serum sodium assays Plasma ADH was measured with radioimmunoassay (3) The results are shown in Table I It will be seen that serum osmolality (measured by the freezing point method) was low ranging from 245 to 275 mosmol/kg H_2O Plasma ADH showed excessively elevated levels (normal value < mosmol/kg H_2O of serum osmolality) with during thirst and a decrease after fluid ad

Other endocrine investigations

Serum FSH prolactin TSH thyroxine and were normal the latter showing an or rhythm During an insulin hypoglycemia te tisol values rose from 542 to 853 nmol/l Serum LH concentration was somewhat lo (normal value 18–125 arb U/l) A TRH te Urinary excretion of aldosterone was norm

Demeclocycline trial

Demeclocycline (Ledermycin®) 900 mg d orally for 8 days Fluid intake was creased from about one to two l/24 h A body weight was unaltered and serum significantly during the treatment period not complain of any subjective symptoms cycline was discontinued her daily fluid duced to about one liter as before

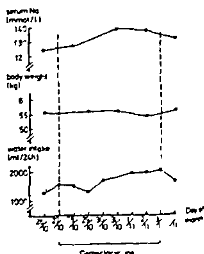


Fig 1 Response to demeclocycline (Le mg daily

DISCUSSION

tient fulfills the criteria of SIADH as sum d by Bartter and Schwartz (1) 1) hypona with corresponding hypo-osmolality of the 2) continued renal excretion of sodium 3) e of clinical evidence of fluid volume deple at is normal skin turgor and BP 4) osmolali e urine higher than that appropriate for the itant tonicity of the plasma that is urine n maximally dilute 5) normal renal function normal adrenal function An additional fea SIADH is that the signs of the syndrome are ed by fluid restriction

he cardinal features of SIADH can be in by administration of vasopressin and water SIADH patients measurement of ADH in and urine after a water load has shown de e levels of the hormone confirming that the ecretion is inappropriate relative to plasma ity (4) Our patient had very high plasma alues even after a water load

cause of the inappropriate secretion of ADH atient is unknown We have not been able to any pulmonary or malignant disease during han one year s observation Furthermore not receive any drugs reported to induce (4) There are several reports on SIADH in tion with different kinds of intracranial le) When the acute phase of the disorder has d the SIADH also promptly disappears (1) ient had an increase of spinal fluid protein indicating some disease of the CNS She ve had encephalitis but the persistence of DH speaks to some extent against this diag t seems likely that the patient has a CNS r resulting in inappropriately high levels of ADH This hypersecretion of ADH ap- to be only partly controlled by fluid intake (Table I) serum osmolality or serum sodium con centration Thus a simple resetting of the osmostat for ADH release (4) could not be demonstrated *The ADH hypersecretion displayed a rather au tonomous pattern*

The patient has a long history of polydipsia pre sumably of the primary psychogenic type Hy ponatremia occurs in rare cases of primary poly dipsia (1) However in these instances urine is nearly maximally dilute and plasma ADH levels are suppressed in contrast to the findings in our pa tient The history of polydipsia may indicate that both the thirst regulating and the ADH regulating centres of the CNS were damaged in our patient

Demeclocycline blocks the antidiuretic action of vasopressin in the renal collecting duct and has *therefore been administered to patients with* SIADH (2) During a short term therapeutical trial with this drug our patient was able to increase her daily fluid intake from one to two liters without untoward effects This effect of the ADH antagoniz ing drug demeclocycline further supports the view that the dilution syndrome observed in our patient was indeed due to inappropriate hypersecretion of ADH

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ANNOUNCEMENTS

The Basel Liver Week will be held at the Mustermesse Basel Switzerland Oct. 3–8 1979 with Dr H Popper New York, as Honorary President. The Liver Week will be centered by the V International Liver Conference which will be presided by Professor D S Sherlock

Further information Prof Dr L. Bianchi Dept. of Pathology University of Basel Schönbeinstrasse 40 CH–4003 Basel Switzerland

The VI Asia Pacific Congress on Diseases of dealing with the medical and surgical aspects of lung diseases and sponsored by the Intern emy of Chest Physicians and Surgeons (Affil can College of Chest Physicians) will be held India, Nov 18–22 1979

Further information Dr A R. B General VI Asia Pacific Congress on Dise Chest, L. D Ruparel Medical Centre Dr An Road Worli Bombay 40025 India

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Coronary Arteriogiaphy in 486 Patients— Arteriographic Pathology and Prognosis

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Ii

ıCT The coronary arteriographic f nd ngs nos s in a series of 486 non surgically treated were analyzed A semiselective inject on was he number and causes of deaths were from the census registry after a follow up f 7–12 years The material comprised normal rams in 26% of the patients wall ir t es at most in 17% obstruction of at least e d ameter in 37% and unclassifiable rams in 19% A mean of 1 8 obstructed per patient was found in the group with ive arterial lesions and among these patients anterior descending artery was most often In the same group the cardiac mortality at ars was 20% There were no significant dif between deceased and survivors with regard al data The arteriograms themselves offered ıformation about the prognosis Normal or wall irregularities at most impl ed excel nosis with regard to death in coronary heart The seven year mortality was 36% among with coronary artery occlus ons which is ntly higher than 14% among those with stenosis Materials from the USA and Cana displayed a much higher mortality than our ı spite of comparable arteriographic f nd ngs

ds coronary d sease/mortal ty coronary ves ography

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s on the long term med cal course of patients ted to coronary arteriography before the in t on of coronary surgery provide an op ı ty to invest gate the natural history of coro- eart d sease The results of such stud es may stabl sh a basel ne prognosis from wh ch to the effect of coronary surgery and other new ɔ es

present report conta ns an analysis of the arteriograph c f ndings in 486 pat ents It also de scribes the extent and severity of the arterial les ons as seen in the arteriographs and their prognost c s gn f cance for mortality

PATIENTS

The study was based on all 510 coronary arteriograph es carried out at Sahlgren s Hosp tal between the beginn ng of 1961 and the m ddle of 1966 Of these 18 were re arteriograph es and were therefore excluded Four pa t ents who had em grated and two who had undergone coronary surgery during the period of cl n cal follow up were also excluded from further analys s wh ch thus comprised 486 pat ents

The nd cat ons for coronary arteriography were primarily to verify the ex stence and degree of coronary artery d sease or coronary heart d sease In 227 pat ents (47%) the cl n cal f nd ngs often nclud ng chest pain suggested coronary heart d sease as one of several d agnost c poss b l es In 148 pat ents (30%) coronary heart d sease was cons dered to be present Coronary arteriography was performed in these pat ents to assess the severity and extent of arterial pathology The rema n ing 111 pat ents (23%) comprised p eoperat ve invest ga t ons of valvular and congen tal heart les ons or d agnos t c stud es in pat ents with hypertens on asymptomat c hyperl p dem a card ac enlargement of unknown cause ECG abnormal t es and d opath c atrial f brillat on

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Present add esses Med cal Cl n c Al ngsås Hosp tal S-441 01 Al ngsås Sweden [2] Med cal Cl n c Borås Hosp tal S 501 15 Borås Sweden [3] Department of Rad ology Beth Israel Hosp tal 330 Brookl ne Avenue Boston MA 02215 USA [4] Astra Lakemedel AB S 151 85 Sodertalje Sweden

Add ess for reprints S Ljungberg Med cal Cl n c Al ngsås Hosp tal S-441 01 Al ngsås Sweden

Abbre at ons R right coronary artery M = ma n stem of the left coronary artery LAD left anterior descend ing coronary artery LCA left c rcumflex coronary artery

Table I *Comparison between distribution of obstructions in 179 of our patients and in 588 patients published by Proudfit et al (17)*

	Our series		Proudfit et al
	N	%	(%)
No of arteries obstructed			
One	86	48	34
Two	50	28	37
Three	36	20	26
Four	7	4	3
Coronary artery			
Left M only	5	3	0 5
Left M with			
LAD	2	1	0 7
LCA	0	0	0 5
R	0	0	1 7
LAD and LCA	2	1	0 9
LAD and R	4	2	2 2
LCA and R	2	1	0 5
LAD LCA and R	7	4	3 1
LAD only	58	32	17 7
LAD with			
LCA	13	7	8.5
R	28	16	16 8
LCA and R	28	16	22 8
LCA only	6	3	5 1
LCA with R	7	4	8 5
R only	17	9	10 5

Clinical data were recorded on admission for coronary arteriography according to principles described earlier (8) The patients ages ranged from 15 to 72 years The mean age was 40 years for patients with normal vessels 51 years for those with irregularities at most 50 years for those with obstructions and 49 years for those with unclassifiable arteriograms Using the same classification of arteriographic findings the ratios of men to women were 2 2 2 0 3 7 and 3 5 respectively

METHODS

All coronary arteriograms were performed using a semiselective injection described by Paulin (16) The validity of this method has been tested by clinical and arteriographic evaluation of 192 patients (16) and by comparison with postmortem findings (8)

The arteriographic changes were evaluated and classified directly after the examination according to criteria described by Paulin (16) No further re-evaluation was made for this study The arteriograms were analyzed with regard to the degree of obstructive lesions and their distribution in the four major segments of the coronary arterial tree the right coronary artery (R) the main stem of the left coronary artery (M) the left anterior descending artery (LAD) and the left circumflex artery (LCA)

The arteries were classified with regard to the degree of pathology as follows 1) No demonstrable der... 2) irregularities without demonstrable lum... 3) Stenosis with diameter encroachment of 5... without demonstrable delay of contrast f... the lesion 4) Stenosis with demonstrable de... filling distal to the stenosis 5) Occlusion

Changes of grades 3-5 were designated a... lesions When patients or arteries were de... ing to the degree of arterial lesions 2-5 the... least one lesion in a subgroup did not exclu... lesions of a lower degree in the same patie... 94 examinations the arteriographs were not ... high quality to allow satisfactory assessme... coronary arterial tree and were therefore de... classifiable

The census registry was used to assess ... among all patients up to June 1 1973 ... causes of death was obtained from death cer... prevalence of autopsy was about 50 ...

The statistical significance of differences be... values was determined by Student's t test ... numbers by the χ^2 test Values of $p<0.05$ we... significant

RESULTS

Extent and severity of arteriographic f...

One hundred and twenty-eight patients ... normal arteriograms 85 (17%) had irreg... most 179 (37%) had obstructions and ... had unclassifiable arteriograms The p... obstructions are classified in Table I and ... the distribution of arteriographic lesion ... patients (48%) had obstructions of one ... the arteries involved were M 6% LAD ... 7% and R 20% Obstructions of two the... arteries were found in 28 20 and 4% ...

Table II shows the severity of obstruc... of the four main arteries The total nu... structed arteries in 179 patients was 32... of 1 8 per patient The LAD alone or ... tion with other arteries was the site of ... in 79% of these patients The M was ... 12% the LCA in 36% and the R in 52% ... with obstructions In the LAD obst... grades 3 4 and 5 occurred about equally ...

Obstructions in the M were of grade 3 ... patients No patient had occlusion in the ... obstructions found in the LCA were of gra... of 65 lesions Only four of 90 occlusions ... the LCA the remaining occlusions were ... approximately equally between the LAD ... Taking all obstructions together the d... degrees 3 4 and 5 was 46% 26% and 2... tively

D str b t on and degree of arter ograpl c obstr ct ons in 179 pat e ts

	No of arteries nvolved				
	Left M	LAD	LCA	R	Total
obs ct on					
w hout delay (grade 3)	18	44	51	35	148
w th delay (grade 4)	4	51	10	19	84
(grade 5)	0	47	4	39	90
	22	14?	65	93	3??
pat ents	12	79	36	5?	
obstruct ons	7	44	20	29	

MORTALITY

the total of 486 pat ents 140 (?9%) had died he postarteriograph c period of 7 12 years III shows the relationsh p between ar ph c f nd ngs and causes of death The mmon cause of death was coronary heart among pat ents with coronary obstruct ons ography or with unclassifiable arteriograms onary deaths occurred among the 128 pa th normal arteriograms and only two (one 2 ne 8 years after arteriography) of 15 deaths the 85 pat ents w th irregularities at most ttributed to coronary heart d sease Non y heart d sease particulary card omyopathy ular les ons was the cause of death among w th normal arteriograms or irregular ves

486 pat ents the cl n cal course was ava l at least seven years It was therefore con appropriate to analyze the mortal ty during iod to supplement the data g ven above and e III wh ch also include the pat ents with follow up The total seven year mortal ty ong pat ents w th normal arteriograms 13% (17 out of 128) wall irregularit es 13% (11 out of 85) obstruct ons 23% (42 out of 179) and unclassif able arteriographs 3?% (30 out of 94)

The yearly mortal ty among pat ents th obstructions is shown in Table IV The mortal ty was high during the f rst year about 8% It fell thereafter and rema ned constant at ? 3% during the fol low ng six years and then rose during the f nal years of observat on

Compar son bet een deceased and se en ear s rv vors nong pat ents l obstr ct e coronary d sease

A total of 88% of those who died and 73% of those who survived had had ang na pectoris or myocar d al infarction as defined earl er (8) The mean rad ograph c heart s ze another s gn of heart d s ease was larger n patients who d ed (899 ml) than in those who survived (790 ml) The mean serum cholesterol was 295 mg/100 ml (7 67 mmol/l) in de ceased pat ents and 306 mg/100 ml (7 96 mmol/l) in survivors Hypertens on def ned as a blood pres sure of at least 160/100 mmHg was more prevalent among non survivors (55%) than surv vors (49%)

III *N mber and ca ses of deatl nt l Ji ne 1 1973 an ong 486 pat ents ho nder ent arter o d r ng 1961–66*

	Arteriog aph c f nd ngs			
of dea h	Normal arteries (*N* 1 8)	Irregu larit es (*N* 85)	Obstruc t ons (*N* 179)	Unclass f able (*N* = 94)
ry heart d sease	0	2	50	?6
onary heart d sease	15	8	2	3
	10	5	10	9
	25	15	6?	38

Table IV *Annual mortality among patients with obstruction at arteriography*

Years after arteriography	No of pats Alive at start	Dead	Mortality (%)
0–1	179	15	8 4
1–2	164	6	3 7
2–3	158	5	3 2
3–4	153	4	2 6
4–5	149	5	3 4
5–6	144	3	2 1
6–7	141	4	2 8
7–8	117	6	5 1
8–9	82	9	11 0
9–10	47	4	8 5
10–11	40	0	–
11–12	20	1	–
12–13	1	0	–

The mean age and the proportion of males were the same in both categories (50 years and 79% respectively) The above mentioned differences did not reach statistical significance

The seven year mortality in relation to the number of arteries obstructed is shown in Table V None of the differences between these figures is statistically significant In Table VI the patients are grouped according to the severity of the obstructions The groups include patients exhibiting at least one obstruction of the stated degree of severity but do not exclude the possibility of concomitant obstruction of a lower degree of severity The difference between mortality figures among those with stenosed and those with occluded arteries is significant

DISCUSSION

Arteriographic findings

Comparison can be justified when criteria used in different studies are similar This applies with respect to our study to that of Proudfit et al (17) who investigated 1 000 patients with a prevalence of normal arteriograms in 27% They found obstructions reducing the diameter of the artery by at least half in 59% of their series This group of patients corresponds closely to the patients with obstructions in our study (Table I) The number of arteries obstructed per patient was 1 8 in our study and 2 0 in that of Proudfit et al (17)

The greatest difference between the two studies is the prevalence of single vessel obs... LAD which was considerably ... among our patients i e 32 vs 17 7 ... site was true for single artery obstr... LCA 3% of our and 5 1% of the ... Proudfit et al When classifying all obstr... respect to distribution and degree Pr... found that 21% of the lesions in the ... plete obstructions were localized to th... result diverges markedly from the find... occlusion group in which the corresp... ure was only 4%

Gensini and Kelly (11) defined ... disease as arteriographic obstruction ... diameter of the vessel by 75% or more ... their 1 263 patients 639 fulfilled this c... these 33% had obstructions in the le... artery and its branches only 7% in the ... nary artery and 58% in both these ... ments When our patients with obstr... grouped in the same way prevalences of ... 42% are found Compared to our study ... by Proudfit et al (17) and Gensini and K... appear to have comprised a higher pr... patients with obstructions in several

In an earlier study Gensini and B... described the angiographic findings in ... 38% of whom were judged to be witho... tive coronary artery disease Among ... patients 68 complete occlusions w... the distribution for the three arteries

Table V *Seven year mortality in rela... number of obstructed arteries*

No of obstructed arteries	No of pats At risk	Dead
One	86	14
Two	50	14
Three or four	43	14

Table VI *Seven year mortality in re... severity of obstruction*

Degree of obstruction	No of pats At risk	Dead
Stenosis without delay	52	7
Stenosis with delay	50	7
Occlusion	77	28

VII *Cardiac mortality after coronary arteriography in patients with obstructive coronary artery*

material of Webster et al (20) five year mortality was calculated from their figure 5 and in that of Brymer et al (6) their figure 1

ea and authors	Mean age at arteriography (y)	Years of observation after arteriography	Cardiac mortality (%)
re Maryland Friesinger et al (9)	≈42	5	27
nd Ohio Bruschke et al (5)	≈50	5	34
		7	56
nd Ohio Webster et al (20)	≈49	5	34
nd Ohio Lim et al (14)	<40	5	29
bor Michigan Brymer et al (6)	≈47	5	31
ne Ontario Burggraf and Parker (7)	≈50	5	27
		7	35
rg Sweden Present study	≈50	5	16
		7	20

mortality Non-cardiac mortality was about 5% of this figure

6% LCA 13% and R 51% When the occlu n our patients are grouped in the same way ures are LAD 52% LCA 4% and R 43% In occlusions were mainly found in the while in the patients of Proudfit et al and n and Buonanno a larger proportion were lo- n the LCA and the R

s our findings differ from those reported with respect to the degree of pathologic find nd the distribution of the most severe arterial The validity of these transatlantic differ calls for further studies

ger and Stary (2) have published a study on pography of coronary obstructions From heart preparations obtained from autopsies med in 14 countries 300 coronary arterial with at least one stenosis obstructing the ter by more than half were selected for the The arterial pathology was assessed by dis n and staining of the preparations Obstruc of one two three and four vessels respec were present in 39 33 25 and 3% of the imens For single vessel obstruction the dis tion among the four main arteries was M 2% 67% LCA 13% and R 18% The mean ber of obstructions per patient was 1 9 The tions of all obstructions were M 7% LAD 44% 20% and R 29% These prevalence figures e remarkably well with those found in the pres study (Table II)

odriguez et al (18) studied 430 hearts using an ction technique They devoted special interest to the presence of occlusions and found a total of 227 with a distribution of LAD 34% LCA 26% and R 39% A higher proportion of occlusions was thus found in the LCA than in the in vivo studies Schlesinger and Zoll (19) found similar results in earlier postmortem studies using a similar injection technique These results may indicate that an oc clusion is particulary deleterious if it involves the LCA

Mortality

Cardiac mortality is the factor with the highest va lidity within individual studies and between dif ferent studies We have therefore chosen to deal mainly with this variable

The high early mortality is not due to arterio- graphic complications (8) being a common phe nomenon in series of patients with progressive disease The increasing late mortality is probably due to an accelerated incidence of coronary heart disease at higher ages

Patient series followed for at least five years after arteriography have been reported from the USA (5 6 9 14 20) and from Canada (7)

Although the above mentioned studies may seem to have provided enough information the present study was undertaken for the following reasons First studies of this type have not been published from Europe Epidemiologic studies have demon strated differences concerning the prevalence and prognosis in coronary heart diseases especially be tween Sweden and other similar countries It is

therefore of interest to analyze groups of patients whose coronary artery disease is arteriographically defined Secondly the selection of our patients was not influenced by surgical considerations or operations either at the time of arteriography or during the subsequent observation time

Table VII presents the published studies with long term follow up and compares the cardiac mortality in patients with obstructive coronary artery disease at five and seven years after arteriography The age and sex compositions of the different studies are similar the proportion of men varies between 73 and 90% and the mean age between 42 and 50 years An exception is the study from Cleveland (14) which comprises exclusively men below 40 years of age

In our study the calculation of cardiac mortality was based on all 179 patients with obstructions The total number of deaths is summarized at five and seven years in Table IV Six and seven non cardiac deaths respectively were subtracted from these figures Among patients with unclassifiable arteriograms in our study the cardiac mortality at five and seven years was only slightly higher 18% and 26% respectively which should not significantly bias the figures of patients with obstructions

Table VII shows that the agreement among the four North American regions concerning five year mortality is good The mean value was about 30% while in our study it was only half 16% The seven year mortality was highest 56% in the Cleveland study (5) and only one third as high in Göteborg 20% while the Canadian study (7) reported an intermediate figure of 35% These differences in mortality are interesting although difficult to explain It might be questioned whether our arteriographic technique which is non selective gives a correct picture of the coronary arterial tree However one would have to postulate a significant overreading of vascular pathology in our material to account for the differences and such a postulate is in complete opposition to the assumption that non selective arteriography should have a lower yield than selective angiographic examinations Furthermore the validity of our technique has been verified in a previous study (8)

The differences in mortality are remarkable in relation to the relatively small differences in arteriographic pathology five and seven years previously

A considerable number of patients were excluded from the North American studies owing to coronary surgery after arteriography This may b
concentration of patients with severe
damage and a poorer prognosis in the
parts of the materials on which the
analyses are based (5) The results may
differences in the natural history of co
disease in different countries This po
suggested by the figures on cause of
sented by the official statistics of S
American life expectancy Thus Björk
out that the mortality for men from all
from coronary heart disease in the U
Sweden for 1963–64 differed consider
age of 50 years for example it was
for the American population It is any
interest that differences between the
Sweden regarding prognosis rather seem
on the state of the myocardium as th
coronary artery pathology seems to be

Comparisons of the prevalence of
tors myocardial infarction hyper
other cardiovascular risk factors at t
arteriography are rendered difficult by
concerning the definition of these
ables

We found that age sex hypertension
cholesterol values registered at the
arteriography had no influence on l
death among patients with obstructions
ence of obesity smoking and glucose t
been found to be of little or no predic
12 15) Previous myocardial infarction
pectoris has not been found to be o
value either in our study or in previo
tions of patients with arteriographic
strated atherosclerosis (5 7 12 15 20

The prognosis is of course poorer
with severe myocardial damage and
compensation shown as cardiac enlarg
demonstrated by ventriculography (5)
urement of the pressure in the left vent
studies including our own in which th
after coronary arteriography has been
indicate that the arteriogram itself con
important information with respect to th
(5 6 7 9 14 15 20) In our patie
mortality during a period of seven
arteriography was twice as high in pa
three or four obstructed arteries compa
in whom only one artery was obstructe
with at least one artery occluded had r

e mortality of those who had no obstruction vere than stenosis without delay The find only the latter difference is statistically ant suggests that it is the degree of the obns rather than the number of arteries ob- which is of importance for the prognosis majority of patients with advanced disease of vessels survived however five years or after arteriography Atherosclerosis of the picardial arteries thus seems to be only one ral components in a complex interplay vascular humoral and myocardial factors under certain circumstances lead to clinical sease or sudden death

rmal arteriogram in the absence of non y heart disease meant a good prognosis de pain or acute serum enzyme and ECG alities suggestive of myocardial infarction arteriography No cardiac death due to rdial infarction occurred in these patients the subsequent 7–12 years This finding is in agreement with the results of previous studies 9 13 15) Patients with only wall ir ities had almost as good a prognosis in our nd in a previous study by others (4) Coroteriography is thus of great prognostic value iction of the outcome for middle aged pa with chest pain of unclear etiology

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Sick Sinus Syndrome Treated with Permanent Pacemaker in 109 Patients

A Follow Up Study

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RACT During the last decade implantation of pacemakers has become the treatment of for patients suffering from the sick sinus syn (SSS) We have followed up 112 SSS patients l with permanent pacemakers in Haukeland al in the period 1966–76 The pacemakers were removed from three of the patients In the re g 109 patients the SSS was characterized by bradyarrhythmias (TBA) in 44 and bradyar mias (BA) in 65 Before implantation, 68 pa had syncopes and 27 severe dizziness After im tion, symptomatic improvement was apparent patients only three still had syncopes During llow up period (mean 34 4 months), 29 patients yearly mortality 9 3%) There was no signifi difference in total mortality between patients TBA and with BA Concomitant disturbances in entricular (AV) conduction occurred in 35 8% patients Among 79 of 80 patients still alive, developed total AV block, 19 had stable atrial ation, 12 of these were possibly pacemaker in ident (ventricular rate >60/min) Systemic em tion was observed in 16 patients, more fre tly in the TBA (12/44) than in the BA group) ($p<0.001$) It is concluded that permanent makers have an excellent symptomatic effect in nts with SSS The prognosis is mainly deter d by the presence or absence of coronary heart se and/or heart failure

words sick sinus syndrome pacemaker treatment nostic factors

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g recent years much of the rapid growth in the of pacemaker treatment can be attributed to ng treatment of patients suffering from sick sinus syndrome (SSS) Although most res report a favourable symptomatic improve t in their patients (3 11 13–16 18 24) reports on the prognosis of the same patients despite pacemaker therapy have been rather depressing (3 10 14 16)

For these reasons we decided to review the pa tient material in our clinic with special emphasis on etiology of the rhythm disturbances prognostic fac tors morbidity after implant and the further de velopment of the rhythm disturbances

PATIENTS

Between 1966 and 1976 a total of 112 patients with SSS had permanent pacemakers implanted Three patients pacemakers were removed after 13 45 and 7 months be cause of wound infections and skin perforations in the former two who were considered pacemaker independent at the time of explantation The third patient demanded to have her pacemaker removed after seven months because she felt it did not improve her condition The first patient died from pneumonia 38 months after removal The two others are still alive 55 and 12 months after explantation

The remaining 109 patients were followed up until Dec 1977 i e for 13–106 months or until death (mean 34 4 months) or for a total of 3755 observation months (312 9 years)

The study comprised 61 males age range 4–88 years (mean 66 2) and 48 females age range 40–90 years (mean 68 4) Mean age of the total study population was 67 2 years or about 3 years less than in our patient series with atrioventricular (AV) block (17) All fulfilled Ferrer s (8) criteria for SSS There was a preponderance of males in the bradyarrhythmia (BA) group (43 ♂ 22 ♀) and a slight female dominance (26 ♀ 18 ♂) in the tachy bradyarrhythmia (TBA) group There was no significant age difference between the BA and TBA groups

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Abbreviations SSS=sick sinus syndrome AV=atrioven tricular BA=bradyarrhythmia TBA=tachy bradyar rhythmia CHD=coronary heart disease TGA=trans position of the great arteries CWS=chest wall stimula tion AF=atrial fibrillation SR=sinus rhythm

Table I *Etiology of rhythm disturbances in the total study population of 109 patients*

	n
Primary arrhythmia	47
CHD	33
Rheumatic valve disease	11
Rheumatic heart disease (without valve lesion)	1
Hypertension	5
Endocrine disorders	4
Cardiomyopathies	3
Collagen diseases	3
Constrictive pericarditis	1
TGA	1

The etiology of the rhythm disturbance is shown in Table I Primary rhythm disturbance was assumed to exist when no other etiological factor could be found Coronary heart disease (CHD) defined as previous myocardial infarction (clinically or on ECG evidence) or a history of angina pectoris showed a male dominance of 23/33 Sixteen patients had a history of previous infarction Patients with rheumatic heart disease with or without valve lesion had a history of previous rheumatic fever Hypertension was defined as diastolic BP exceeding 95 mmHg or need of antihypertensive medication Two of four patients with endocrine disorders were hypothyroid one was hyperthyroid and one had tuberculosis and Addison s disease All three cardiomyopathies were congestive Two of the patients with collagen disease had polymyalgia and one had rheumatoid arthritis Our youngest patient was a 4-year-old boy with operated transposition of the great ries (TGA)

(68 patients) and dizziness/near syncopes patients) were the main indications for implanting naker Nine patients received pacemakers because ı serious heart failure with slow rhythms three had TBA that could not be controlled by medication alone and two occasionally had extreme bradycardia down to 20 beats/min with anginal attacks Other symptoms noted were palpitations (35 patients) heart failure (29 patients) and exertional dyspnea (30 patients) The 109 patients were grouped according to the New York Heart Association as follows class I 27 patients class II 57 classes III–IV 25 patients

The heart size was normal in 59 patients enlarged in 50 i e cardiothoracic ratios exceeding 0 5 or relative heart volumes exceeding 550 ml/m² in males and 450 ml/m² in females

METHODS

The rhythm disturbances were documented by repeated 12 lead ECG recordings telemetry or provocative tests like sinus node recovery time or carotid sinus pressure

When more than one arrhythmia was present the dominant one is listed AV conduction defects were found from repeated ECG recordings at the time of pacemaker implantation Conduction defects from digitalis or antiarrhythmic drug toxicity and electrolyte disturb excluded

All pacemaker implantations were performe Surgical Department Haukeland Hospital dial implantation route was preferred in all cas the boy with TGA for whom a myocardial chosen One patient with congestive cardiom probably diphtheric and gross cardiac enlargeme change to a myocardial electrode because of unst trode position Three patients were equipped rate pacemakers 97 with QRS-inhibited and QRS triggered Pacing from an atrial site employed

Our follow up study covers all 109 patients co One patient died postoperatively from ventricul tion that occurred during catheter manipulation the patients were followed at regular three mo vals in the Outpatient Clinic Twenty five pat regularly controlled in local hospitals or by t doctors who consulted us if problems arose Th ments were performed in our hospital Three have moved out of the region but their doctor request supplied the information needed

We have been able to study the developme rhythm disturbance and conduction de pacemaker treatment in 79 of the 80 patients ECGs were recorded at least twice during th months of the study at three month intervals with exclusively pacemaker rhythm or pacemaker and spontaneous heart activity stimulation (CWS) was performed to study the heart rhythm In five patients living far from th CWS was performed only once At the time of we did not have access to 24-hour tape monitor fore the rhythms are listed as stable if they exis or more check ups over more than a three mont

Of the 21 patients who died in hospital 11 sied Detailed examination of the atria and c systems has not been made For patients who d hospital the cause of death has been obtained cial death certificates Concerning the patients suddenly outside hospital we interviewed close when possible or the doctor who had signed certificate

Fisher Irwin test for two-by two tables (1) used for statistical analysis

RESULTS

Morbidity

Of the 109 patients 104 (95 4%) exp marked improvement of their symptom showed no change and one died The most able results were found in patients with syn dizziness Syncopes persisted in only thre 68 patients—two males with CHD who suddenly (both autopsied) and one female thostatic hypotension Four patients st plained of dizziness—two of them had

II *Drug treatment before and after perma- acemaker implantation*

	Before (*n*)	After (*n*)
s	40	70
hythmic drugs/β blockers	20	7
thicomimetic/anticholinergic	39	1
cs	28	35
agulants	1	3

s one died from infarction after three months ue from metastasizing carcinoma of the pros whether also cerebral is not known

two patients with extreme bradycardia and l attacks lost their symptoms Two of the atients classified as unchanged belonged to onal classes III–IV Most patients with heart experienced some improvement perhaps e of the more liberal use of digitalis ides after pacemaker implantation Drug ent before and after permanent pacemaker itation is specified in Table II The seven ts still on antiarrhythmic drugs were TBA ts in whom the arrhythmia could not be con by pacemaker/digitalis therapy One female t with orthostatic hypotension is still on sym omimetics

lve patients (27 2%) in the TBA group had a of 17 embolic episodes nine of which took before pacemaker implantation Three pa experienced their embolic episodes after im tion and five both before and after Two died one from pulmonary and one from intestinal em bolism both were autopsied For the remainder the diagnosis of the embolization was established on clinical grounds alone

Only four (6%) of the patients in the BA group had embolic episodes in contrast to 27 2% in the TBA group The difference is highly significant ($p<0\,001$) Four of the patients who experienced embolic episodes had valvular heart diseases one of them was on anticoagulant treatment Eight more patients had cardiac enlargement with involvement of the atria Only four patients had normal heart size

Rhythm studies

At first implant 39 patients (35 8%) had concomi tant disturbances in the AV conduction (Table III) with no great difference between the BA and TBA groups

The dominant rhythm at follow up in relation to rhythm disturbance before implantation is shown in Table IV Of the five patients who later developed total AV block two had signs of trifascicular dis ease and three intermittent AV block II–III at the time of implant Four patients with intermittent AV block II–III showed only pacemaker rhythm at fol low ups Three of them died before our study started the fourth is confined to bed in a nursing home and is the only one alive whom we have not been able to follow up

Nineteen (24 1%) of the 79 patients studied had developed stable atrial fibrillation (AF) Two addi tional patients had AF at follow up but as we were

III *Rhythm disturbances before pacemaker implantation*

sinoatrial block SA – sinus arrest HCS = hypersensitive carotid sinus AVJR = atrioventricular junctional n CSR = coronary sinus rhythm SB = sinus bradycardia IM = intermittent RBBB = right bundle branch block (bifascicular) = left bundle branch block (LBBB) or AV block I + RBBB TFAS (trifascicular) AV block I + or AV block I + RBBB + left anterior hemiblock

nant rhythm bance f pats)			Concomitant AV conduction defect (no of pats) AV block I	RBBB	BFAS	TFAS	IM AV block II–III	Total
oup		65						
B SA HCS	49		5	2	5	3	6	
JR CSR	7		1					
	9		1	1				24
group		44	3	1	4	1	6	15
l		109	10	4	9	4	12	39

Table IV *Heart rhythm at follow up compared with rhythm disturbances at implantation in 79 survivors*

Original rhythm disturbance		Heart rhythm at follow up: AF <60/min	AF >60/min	TBA	BA	SR >60/min	AV block III
BA	47	1	2	1	27	14	2
TBA	32	6	10	3	5	5	3
Total	79	7	12	4	32	19	5

able to perform CWS only once their rhythms are not listed as stable In the TBA group 16 (50%) of 32 patients had developed AF vs three (6 8%) of 47 in the BA group a highly significant statistical difference ($p<0\ 0001$) These three patients in the BA group had enlarged hearts at implantation with involvement of the left atrium

We did not find any significant difference in the mean observation period between those who did and those who did not develop stable AF in the TBA groups (40 4 vs 39 1 months) Ventricular rates were above 60/min in 12 of the patients with stable AF and should theoretically be managed on digitalis/antiarrhythmic treatment alone Decision not to replace the pacemaker was made only once The patient concerned has now been followed for three months

Mortality

Twenty nine patients (26 7%) died during the follow-up (Table V) giving a yearly mortality rate of 9 3% The mean age of the patients who d[…] 69 8 years (males 68 3 females 72 2) Th[…] difference in sex linked mortality in th[…] (31%) males and 10/48 (20 8%) females […] male excess mortality may be due to th[…] prevalence of and mortality from CHD […] males Compared to the total study pop[…] found a significantly higher mortality 15/[…] 33 among CHD patients ($p<0\ 001$) Twel[…] deceased CHD patients were males 10 […] tory of previous myocardial infarction

There was no significant difference in […] tality between the TBA group in which 1[…] of 44 died and the BA group in which 1[…] of 65 patients died The BA and TBA gro[…] comparable since the number of deaths […] tients with CHD in the BA group is far gr[…] in the TBA group 12 vs 3 patients (Table[…]

Nineteen (38%) of 50 patients with […] heart size and 11 (44%) of 25 patients in […] classes III–IV died Both these groups […]

Table V *Mortality*

Primary = primary cause of rhythm disturbances Collagen = collagen disease CP = constrictive pericard[…] aortic stenosis MS = mitral stenosis

	BA group	TBA group
Cardiovascular		
Sudden death	4 (3 CHD 1 AS)	3 (2 CHD 1 MS)
Acute myocardial infarction	3 (3 CHD)	4 (2 Primary 1 CHD 1 Coll[…]
Chronic heart failure	3 (3 CHD)	1 (Primary)
Ventricular fibrillation	1 (CHD)	0
Cerebral stroke	3 (2 CHD 1 Primary)	0
Pulmonary embolism	0	1 (Primary)
Intestinal embolism	0	1 (Primary)
	14	10
Cancer	3 (1 Primary 1 Collagen 1 CP)	0
Pneumonia	0	2 (1 Primary 1 MS)
Total	17	12

ly poorer prognosis than the whole series ? and $p<0\ 01$)

ne eight patients with all these three major tors seven died after a mean observation of 15 months (range 0–47) One patient is ve after 35 months Rheumatic valve disease seem to have any major effect on prognosis l died 30 3%) nor did the cardiomyopathies

three (10%) of 30 patients with primary i disturbance and no signs of heart enlarge or functional deterioration beyond class II This gives a yearly mortality rate of 3 5% red to 2 7% in the Norwegian population djusted to sex and age (5)

major cause of death (82 8%) was cardiovas Table V) Of the seven patients who died ly and unexpectedly five had advanced one mild aortic and one mild mitral valve All seven patients died outside hospital and tual causes of the sudden deaths are not Two autopsies were performed and ad i CHD with previous infarction was diag in both cases No new infarctions were found eir pacemakers functioned normally One ssume that the cause of death was cardiac imias The two patients who died from em pisodes belonged to the TBA group and were ied Three patients in the BA group died from al strokes They were autopsied and none iboli

DISCUSSION

1971 patients with SSS constituted only of our patients treated with permanent akers (16) With the introduction of demand iakers and a better understanding of the seri ss of the syndrome this percentage has in d to 40 5 during 1972–76 Other authors re percentages of 11 5–47 (11 13 18) The seri ss of the SSS is reflected by the fact that % of our patients had had Adams Stokes es Another 24 8% were severely incapaci by dizziness/near syncopes Forty nine pa (45%) had a temporary pacemaker implanted ise of life threatening symptoms

ere seems to be no general agreement about diseases are of etiological importance for the m disorder Davies and Pomerance (6) have nstrated degenerative changes in the atria and sinus node starting at the age of 60 which may explain a primary cause of the disease Our figure of 43 1% (Table I) agrees well with that of Shaw and Kekwick (21) who reported primary arrhythmia in 47% of their patients Others have considered CHD the most important etiological factor (11 23) with figures ranging from 24 to 61% The incidence of rheumatic heart disease varies from 11 to 20% (20 21) and some authors have found a relatively high incidence of diphtheric cardiomyopathies (19 21)

There are divergent opinions on sex distribution (10 11 13 17 19 23) probably because the patient groups are small We found a small male dominance of 61/48 which corresponds well with 2/1 found by Shaw and Kekwick (21) among more than 400 patients with suspected or established SSS

Like most authors (10 11 13 17 19 21 22) we noticed an excellent improvement of complaints like syncopes and dizziness Residual complaints could be explained by coexisting diseases not related to sinus node dysfunction The effect on heart failure was less convincing possibly because of the loss of atrial contribution

The occurrence of systemic emboli has been a controversial matter Fairfax et al (7) found embolic episodes in 20% of patients with TBA vs 4% of patients with BA and in 1 3% of patients with AV blocks Bathen et al (4) found embolic episodes in 35% in the TBA group 7% in the BA group and 10% in the AV group some authors report 21–48% in TBA patients (3 17) while some others (10) found no embolic episodes in 50 patients with BA There is an uncertainty regarding these studies as the diagnosis of embolic episodes is given in most cases on clinical grounds alone but as the authors point out the bias would at least be the same in all groups We have also found a significantly higher incidence of suspected embolic episodes in our TBA patients 27 2% vs 6% in the BA group In our AV block series (17) we found a mortality of 5% from pulmonary embolism while 10% died from cerebral stroke The latter figure corresponds with that found in this study Bathen et al (4) found that 10 out of 14 embolic episodes occurred after pacemaker implantation Radford and Julian (18) on the other hand found that 8 out of 10 embolic episodes occurred before pacemaker implantation Embolic episodes before and after implantation were more equally divided in our series (9 before 8 after)

All the papers quoted indicate that the

mechanism of the embolic episodes can be attributed in most instances to changes between tachy- and bradyarrhythmia. It seems therefore desirable to follow these patients closely in the immediate postoperative period in order to find the best antiarrhythmic regimen. Whether this should be preferred to permanent anticoagulant treatment needs to be further elucidated. Four of our patients had valvular heart disease for which the indication for anticoagulant therapy had already been established. One patient with aortic valve prosthesis in the BA group nevertheless had an embolic episode although he was on adequate anticoagulant therapy. Another eight of the 16 patients had enlarged heart with involvement of the atria and only four had normal heart size. At the moment we do not give prophylactic anticoagulant therapy routinely to our TBA patients. We are led to believe that anticoagulants should be given only to patients with heart valve disease or enlarged heart and not routinely as recommended by some authors (4, 7, 18). Only a prospective study, however, can give a more definite answer to this question.

Little is known about the natural course of the SSS. Ferrer (8) states that it probably takes 5–10 years before the sinus node is completely destroyed by degeneration. Amikam and Riss (2) define three different forms: 1) a subacute with TBA, CHD and poor prognosis; 2) a transient with spontaneous cure by development of stable AF, equally divided ... TBA and BA groups; 3) a chronic with and good prognosis.

This is in contrast to our experience. We found highest incidence of CHD in the BA group which would have an unfavourable effect on prognosis. Furthermore, we found that the tendency to develop stable AF was more pronounced in the TBA group (Table IV). This seems to indicate that TBA may be considered the transient form of the syndrome. Of 56 patients with BA reported by Vera et al. (23), 11 have developed stable AF after a mean observation period of 3.2 years. Those who did not develop AF were observed for a much shorter period (1.9 years) than those who did (5.5 years). Ten of the patients are now considered pacemaker-independent. There was no great difference in observation periods between those who did and those who did not develop stable AF in our TBA group. Twelve of our 19 patients who developed stable AF had adequate ventricular response (>60/min) and may now be considered pacemaker independent.

Studies with Holter monitoring now in ... may throw more light on this point.

Narula (15) found that 67% had conco... conduction defects in a patient group w... bradycardia. Our figure of 35.8% corresp... with that of Härtel and Talvensaari (12). T... seems to be a significant overlap between ... and the AV conduction defects.

Theoretically it would be ideal to estab... pacing. Some authors (9) claim that AV s... would be beneficial in 77% of the pa... treated patients. The great number of ... rhythm disturbances may, however, be a ... jection to a more liberal use of atrial p... single cases AV synchrony may be critic... due to a marked fall in cardiac output (... recently shown (1), due to atrial reflexes a... tion of peripheral resistance.

AV sequential pacing is indicated for ... patients. Because of the complexity ... pacemakers, they should only be impla... thorough hemodynamic investigations. I... without heart failure we have instead ... programmable ventricular low rate pa... thus saving the patients from syncopes an... their hearts to work in a physiological wa... the time.

Death rates differ widely between stud... 22, 24) but are hard to compare as the ... for implanting pacemakers also differ w... clinic to clinic. We found that the patients ... earliest years of implantation had a better ... than those from the later years, probably ... a more liberal use of pacemaker treatment ... and more critically ill patients in recent ... found a yearly mortality rate of 9.3% and ... year it was 9.2% (10/109). We noted a ... dence of unexpected sudden death—7/... vs. 11/60 (18%) in our AV block study ... may be ascribed to the higher incidence o... SSS than in AV block patients (17, 18) an... that pacemaker treatment does not preve... from probable cardiac arrhythmias.

Like Skagen and Fischer Hansen (22) ... that when we subdivided our patients ... groups—one with CHD and/or serious hea... or cancer, and one without—the yearly ... rate in the latter group was close to that o... and age adjusted Norwegian population ... seems to confirm that SSS per se is no... prognostic factor.

CONCLUSION

ents with SSS now account for almost half of ients in our pacemaker clinic 2) Stable AF nts a spontaneous cure of SSS TBA seems the intermediate form of the syndrome 3) aker implantat on has an excellent effect on ›es and dizziness but only minor effect on ailure 4) CHD is more frequent among pa with SSS than with AV block a factor which to influence l fe expectancy Coexisting heart and not SSS per se is of importance for the ›sis 5) Coexisting AV conduction defects mmon It will together with the development make pacing from an atrial site less recom ble as a routine method 6) Systemic embolic es are signif cantly more common in patients BA than with BA It is noteworthy that out of patients with one or more embol c episodes our had normal heart size Prospective stud es ded before a definite answer can be given to estion whether or not long term anticoagulant y will have a beneficial effect

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Aortic Valve Replacement in Elderly Patients

Ole Storstein and Leif Efskind

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ACT During the years 1965-75 98 patients ian 65 years of age had aortic valve replace- our hospital 24 ball valves and 74 disc valves l in their aortic orifice Actuarial analysis of l in these patients shows that the operative slightly higher in elder than in younger pa The survival curve for the following years for ho had disc valve implantation runs parallel of younger patients while those who had ball nplantation showed a more rapid fall in survi r 3 years *After 10 years only 30 % of patients* ll valve transplantation were alive

ds aortic valve surgery elderly patients

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valve replacement is a well established utic procedure in the treatment of severe valvular disease Follow up studies of pa operated on at Rikshospitalet Oslo for aortic lisease have shown an operative mortality of l 15% and a late mortality of 10% (11) In ears the operative mortality has fallen to 11 % These figures must be weighed against the prognosis for patients with severe aortic is associated with ominous symptoms like pectoris paroxysmal dyspnea and syncope tic valve disease and especially aortic ste ows an increasing incidence with increas This is partly due to the pathoanatomical occurring in congenital bicuspid aortic with increasing age and partly due to the form of *aortic stenosis which is seen* patients with increased fibrosis and calci of aortic valves

hospitals there has been a reluctance to on elderly patients more than 65 or 70 years 5) The reason for this has been a fear of high lity both at operation and in the following years Others are of the opinion that elderly patients should be offered the same possibility of treatment as younger ones (1 2 9)

PATIENTS AND METHODS

To study this problem we have reviewed patients more than 65 years of age who have had aortic valve replace ment at Rikshospitalet Oslo Altogether 98 patients 62 men and 36 women have been operated on during 1965-75 *Twenty four of these had ball valve implantation in* most cases Starr-Edwards ball valve in 1965-70 while 74 had disc valve implantation either Bjork-Shiley or Lillehei-Kaster valve in 1971-75 As shown in Table I most of the patients were between 65 and 70 years only a few more than 70 years old The oldest patient was 73 years

The follow up was completed by Jan 1 1977 with an observation period ranging from 1 to 11 years The fate of the patients has been studied by questionnaire to the pa tients doctors The actuarial method (4) has been used to analyze the survival in these patients Those who had been operated on during 1965-75 have been analyzed separately for each year These groups have then been *lumped together to calculate the cumulative proportion of* surviving patients In this way we get a survival curve from year to year These survival curves have been com pared to the survival curve for the Norwegian population according to mortality statistics from the years 1973-74 matched for sex and age

RESULTS

Fig 1 shows the survival curve for patients with aortic ball valve implantation aged more than 65 years at operation This curve is compared to the *corresponding survival curve for patients* less than 65 years old and the survival curve for the Nor wegian population with the same sex and age dis tribution Elderly patients have been followed for up to 11 years the younger for only up to 5 years Both groups of ball valve implantation show a mor tality of 20-25 % during the first year Later the

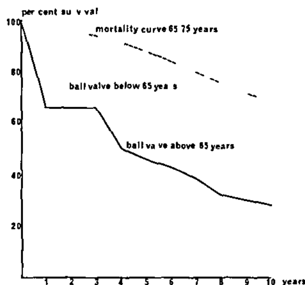


Fig 1 Survival curve for pat ents with aortic ball valve replacement below and above 65 years compared to the mortality curve for the Norwegian population of corresponding age

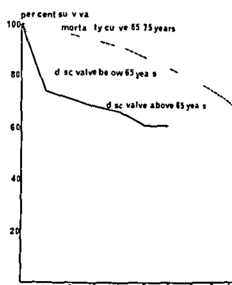


Fig 2 Survival curve for patients with d sc valv tation below and above 65 years compa ed to the curve for the Norweg an population of corre po

curve for the younger patients flattens out while elderly patients show a rather rapid fall from the third year on After 10 years only 30% of the elderly patients are alive

Fig 2 shows the corresponding curves for patients who had disc valve implantation The observation period for the elderly patients is up to 6 years and for the younger up to 4 years A considerably ler difference in survival between younger and patients is evident After 4 years the differ is only 6%

DISCUSSION

Only a few studies have been made previously on the fate of elderly patients operated on with aortic valve replacement In 1969 Ahmad and Starr (2) studied 63 patients more than 60 years of age who had a Starr–Edwards prosthesis implanted in the aortic ostium The operative mortality in this group was 19% and the late mortality 9% These percentages are within the same range as those of patients in the younger age group The oldest patient in their series was 75 years old and he was doing well 3 years after aortic valve replacement Ahmad and Starr in their above mentioned study recommended that age should not be contraindication to valve replacement Acar et al (1) reported on 33 patients who had aortic valve replacement after 60 years of age The operative mortality was h viduals more than 60 years of age 26% to 18% in individuals below that age Th mortality was mainly due to the greater pr of coronary artery disease in the older ag Oh et al (9) studied 73 patients who h valve replacement after 60 years of age mortality was 15% and late mortality 10% was a functional improvement in 77% ing patients and the majority were able to work The writers conclude that althou mortality was higher than in younger pa derly patients should be offered the same in view of the serious prognosis for pa already are severely incapacitated from aor disease Fishman et al (6) found the same mortality (15%) among 100 patients above of age subjected to valve replacement as younger patients (14 3%) During the last the postoperative mortality had dropped De Bono et al (3) studied 40 patients age years who had aortic valve replacement them disc valve implantation in 1973 76 of these patients died in the postoperat and none in the follow up period of 1 3 yea

This study shows that aortic valve impl in patients more than 65 years of age can out with a tolerable risk The operative ris considerably greater than for younger pat en

Age distribution at operation

	N
	20
	19
	13
	24
	13
	3
	3
	2
	1
	98

rm follow up shows that among patients who c valve implantation the survival is almost as or elderly as for younger patients while the ty increased rapidly from the third year on patients with ball valve implantation The for a better prognosis in disc valve than in lve implantation is not clear The difference due to the fact that the patients had been ed on in different periods because the im l survival after disc valve implantation also to patients in the younger age group It may due to better hemodynamic performance by alve than by ball valve *prosthesis It is* orthy that Starr and Lawson (10) presented a al curve from 1972–74 for 221 patients over 60 with isolated aortic ball valve replacement is almost identical to our curve presented in

le II shows that the causes of death among patients both for hospital and late mortality ot much different from what we have found g younger patients in an earlier study (11) The causes of hospital mortality in both series myocardial failure arrhythmia and infection deaths are predominantly due to myocardial One should perhaps have expected a higher lity from myocardial infarction for elderly for younger patients but there is as we see stinct difference between the two series and vely few died from myocardial infarction As ll known changes in the coronary arteries ase with increasing age These changes have studied *in patients with* aortic stenosis by ock (7) He found by coronary angiography icant stenosis in one or more coronary arteries % of 133 patients under 40 years with aortic sis in 60% of those aged 40–60 years and in

Table II *Causes of death among patients in the present and a previous study (11)*

	Early	Late	Total
Present study (n=98)			
Heart failure	6	13	19
Arrhythmias	5	0	5
Infection	3	0	3
Myocardial infarction	3	2	5
On the table	3	–	3
Embolism	0	3	3
Carcinoma	0	2	2
Total	20	20	40
Previous study (n=243)			
Arrhythmia	12	0	12
Myocardial failure	14	3	17
Sepsis infection	6	6	12
Myocardial infarction	8	1	9
Embolism	1	4	5
Aortic rupture	0	1	1
Unknown	0	4	4
Carcinoma	0	1	1
Total	41	20	61

68% of those older than 60 years Coronary arterial stenoses were found more frequently among patients with angina pectoris namely in two-thirds but even among patients without angina pectoris significant stenosis of one or more coronary arteries were found in one third In a previous study of 100 patients with aortic valvular disease significant coronary artery stenosis was found in 25% mainly in the age group 60–69 years (12) In these older patients there are also other causes of death predominantly carcinoma Two deaths due to cancer occurred in the present series during the follow up period

CONCLUSION

This study shows that patients more than 65 years of age may be operated on for aortic valve disease with valve implantation on the same indications as younger patients With the disc valves which are used today the elderly patients do not run any significantly higher risk of operative or late mortality than the younger

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Prediction of Survival in Patients with Acute Myocardial Infarction

A Clinical Study on 100 Consecutive Patients

G Biorck L R Erhardt and G Lindberg

From the Department of Medicine Serafimerlasarettet Stockholm Sweden

ACT Expected survival after acute myocar rction (AMI) in 100 consecutive patients was d by three doctors and two nurses at the time arge from a CCU Predictions were compared rious coronary prognostic indices (CPI) and and to be too optimistic for the first 9 months nced physicians made more reliable pre than junior physicians and nurses All pa ith a predicted survival of more than 10 years ve after 1 year and all with predicted death one month died during the first year Inter predictions were unreliable with reference to year survival Regardless of which CPI was low index score carried a very low one year ty and high index a high mortality Inter index scores were unreliable A comparison the predictions and index scores showed that as no difference in sensitivity and specificity the methods Our study thus shows that pa with either a very good or a very poor prog ill be identified regardless of the method used oblem of identifying the individual with an diate risk remains to be solved

rds acute myocardial infarction prognostication y prognostic index subjective estimate receiver ng curve

ed Scand 206 165 1979

ble prognostic judgement would greatly help ts families and physicians in the management ents with acute myocardial infarction (AMI) us coronary prognostic indices (CPI) have used to predict survival in patients with AMI 6) However these CPIs only indicate the e likelihood of being dead or alive after a cer eriod They have not permitted a prognosis as expected survival in an individual patient

primary purpose of our study was to investi whether members of a coronary care unit) staff guided only by their clinical impression of the patient and results of routine laboratory tests could estimate the survival time for patients with AMI Secondly we aimed at comparing the results of these estimates with those of three CPIs The predictions and outcome were evaluated after one year

PATIENTS AND METHODS

The study group consisted of 100 consecutive patients with AMI treated in the CCU at Serafimerlasarettet Stockholm between Aug 1975 and May 1976 Six patients suffered re infarctions and were seen twice There were 68 men (mean age 67 2 years range 31–82) and 32 women (mean age 70 1 years range 56–85)

At the time of discharge from the CCU usually after 48 hours treatment three doctors (the head of the CCU a junior and a senior resident) and two nurses (the head nurse and a research assistant) predicted each patient s probable length of survival according to seven categories 1) More than 10 years 2) 5–10 years 3) 1–5 years 4) 3–12 months 5) 1–3 months 6) 1–4 weeks 7) less than one week All variables needed to calculate the three CPIs were collected continuously without the knowledge of the staff The most complex index as presented by Peel et al (6) includes seven parameters (sex age previous history shock heart failure ECG and heart rhythm) The long term CPI of Norris et al (5) is based on age previous history heart failure and heart size The long term CPI presented by Helmers (1) utilizes only two variables—age and respiratory rate on admission to the CCU

During the study period 492 individual predictions were performed and a *mean predictive value* was calculated for each patient In order to compare the prognostic ability between different members of the staff we applied a method derived from information theory (4) The individual estimates of expected survival and the various in

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Abbreviations AMI = acute myocardial infarction CPI = coronary prognostic index CCU = coronary care unit ROC = receiver operating curve TP = true positive FP = false positive

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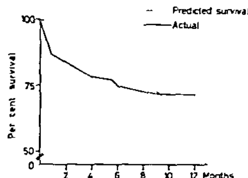


Fig 1 Mean actual and subjectively predicted cumulative one year survival in 100 AMI patients

dex scores supposedly carry some information about the patient s prognosis With respect to one year survival all individual predictions were categorized as true or false positives or true or false negatives True positives were predictions of death within one year (categories 4–7) which matched with death False positives were predictions of death in patients who survived Such categorization made it possible to calculate the information content of subjective estimates of different observers The information content was calculated as the *average reduction of uncertainty* using the formula of Nishiyama et al (4)

The receiver operating curve (ROC) technically described by Metz et al (3) was used to compare the prognostic value of subjective estimates with the value of index scores When using index scores to predict the prognosis of individual patients a cut-off point along the score range must be chosen An index score above this point will forecast a poor prognosis (death within one year) while scores below the cut-off point will indicate a good prognosis (survival more than one year) If a very low index score is chosen as the cut-off point a large number of patients with a favourable prognosis will receive the same prediction and vice versa, corresponding to a change in the relation between sensitivity and specificity The proportion of accurately predicted patients with poor prognosis is called the TP ratio The false positive (FP) ratio is the proportion of patients with good prognosis falsely predicted to have a poor prognosis The ROC curve monitors the changes in these ratios when the cut-off point is moved along the index score range The ROC curve for the subjective estimates was constructed from cut-off points for the seven classes of the length of probable survival

RESULTS

During the first year 29 patients died (28 of myocardial infarction and one of aortic aneurysm) Fig 1 shows the survival curves derived from the mean predicted values and from actual events Predictions of short term prognosis were too optimistic for the first 9 months A comparison with the actual survival after one year revealed that none of the patients predicted to survive more than … had died (Fig 2) At the other end of the scale all patients predicted to survive … weeks had died within one year Obviou… tive prediction adequately identifies p… very good or very poor prognosis In… diction of the short term prognosis betw… 12 months was very unreliable (Fig 2) L… with a predicted survival of 1–12 mo… chance of being alive after one year was… mately 50%

The same tables were constructed for t… year survival in relation to the index scor… three CPIs (Fig 3) Like subjective predic… index scores were valuable for identifying… with very good or very poor prognosis… intermediate index scores were very un… regards one year survival

Table I shows the average reduction of u… ty about one year survival that was provid… predictions of different members of the st… reduction of uncertainty when all predictor… included was 0 860 As can be seen a se… cian put forward the most reliable predic… ducing the average uncertainty by 0 272 On… physician s predictions were only sligh… plausible than those expected from th… coin his average reduction of uncertai… only 0 005 When the subjective estimate… grouped by staff categories the senior p…

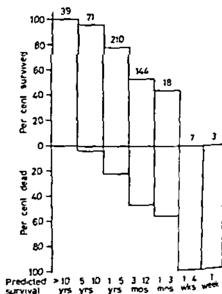


Fig 2 Actual survival after one year compared … subjective predictions Figures above the bars indic… number of predictions made in each category

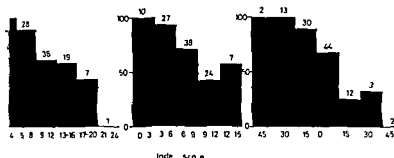


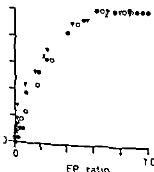
Fig 3 Actual survival after one year compared with the index scores of CPIs of Peel et al (6) Norris et al (5) and Helmers (1)

ed the highest information content in their tions (0 207) followed by their junior col s (0 082) and the nurses (0 044)

4 shows the ROC curve for the subjective tes as well as for the three CPIs The end of the curve for subjective predictions are d from hypothetical cut-off points where ind all of the estimates respectively are con d to forecast a poor prognosis i e death with year There was no difference between the derived from index scores and the curve for tive estimates On the contrary they seemed n a common curve This means that the same ivity and specificity was found regardless of tive method

DISCUSSION

tudy thus shows that clinical judgement and e of CPI scores are equally good or bad for ısting the one year survival of patients after an As might be expected the individual predic were too optimistic with regard to short term osis Obviously psychological mechanisms be involved and it is probably only natural to



4 ROC curve showing cut-off points from subjective ction (×) the CPIs of Peel et al (O) Norris et al (●) Helmers (∇)

reject a prognosis of imminent death regardless of which disease is involved

The similarity between individual prediction of prognosis and the CPI scores deserves some comment Since the CPI score does not predict the time of death but rather indicates the relative risk of being dead after a certain interval it may not be correct to compare it with individual predictions It was assumed that in respect of one year survival the individual predictions worked as an ordinate discrete variable reflecting the probability of survival An estimated survival of more than 10 years was supposed to bring a higher probability of living longer than one year than would an estimated survival of 3–12 months This assumption made it possible to apply the ROC curve technique

When comparing the prognostic results of individual predictions and CPIs two further points should be considered The first is that the ROC curve describes the changes of error rates as the cut off point is moved along the test scale or as in this case the index score Although the ROC curve

Table I *Average reduction of uncertainty regarding one year survival provided by the subjective predictions of different members of the CCU staff*

CCU staff member	Average reduction of uncertainty (bits)
Senior physician	0 272
Nurse	0 165
Junior physician	0 151
Senior physician	0 134
Junior physician	0 118
Nurse	0 095
Junior physician	0 065
Nurse	0 016
Junior physician	0 005
Total	
Senior physicians	0 207
Junior physicians	0 082
Nurses	0 044

does make it possible to compare error rates over the whole scale it still provides only a comparison between error rates As pointed out by Shapiro (7) an error rate comparison does not take into account the magnitude of an error Furthermore a false negative and a false positive prediction might not be of the same value or utility The utilities can however be crucial for the choice of the cut-off point (7)

Knowledge of CPIs among the participants especially that of Helmers (1) may be one explanation for the similarity found between individual predictions and CPIs There was however no difference in this respect between the doctors who were familiar with these indices and the nurses who were not Furthermore no mutual influence among the participants was possible since all predictions were performed individually The best predictions were made by a senior physician and a head nurse the latter with several years experience in the CCU Whether this ability to prognosticate was due to a greater familiarity with the CPIs or to clinical experience is difficult to decide

To conclude our study has shown that regardless of the method used patients with very good or very poor prognosis can be adequately identified The problem of identifying patients with an intermediate risk remains to be solved

ACKNOWLEDGEMENT

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Early Mobilızatıon and Dıscharge of Patıents wıth Acute Myocardıal Infarctıon

A Prospect e St d\ Us ng R sk Ind cators and E rl\ Exercıse Tests

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.ACT Consecut ve patıents (*n* 184) survı\ hours in a coronary care unıt were dıvided ·e rap dly (RM) (*n* 55 30%) and one conven mobil zed (CM) group (*n* 129 70%) The n of RM pat ents was based on the absence of rl\ rısk ind cators (RI) reflectıng electrıcal chan cal heart dysfunctıon During after-care RIs were evaluated ıncluding a submaxımal t exercıse test to 50 W which excluded nıne add t onal pat ents from the RM group After ng four patıents for non-card ac reasons the ıng 42 RM pat ents were rap dl\ mob lızed charged after a mean of nine da\s in contrast ·ean of 19 days ın the CM group comprısıng ıents No RM pat ent died ın hospital and onl\ tıent d ed durıng a sıx month follow up com to 17 ($p<0.01$) and 28 ($p<0.01$) pat ents re- ely ın the CM group Both reinfarctıon and ıt\ ıncreased with the number of posıtı\e RIs rl\ exercıse test excluded four pat ents from 1 group Altogether 22 of 45 patıents showed ıbnormal tv durıng exercıse Half of these 22 were readmıtted due to cardıac complıca the follow up perıod These findıngs · that ıt ıs possıble to ıdentıfy a group of w th AMI suıtable for early dıscharge and early exercıse test in selected good rısk pa is safe and ıdentıfes a group prone to com ons durıng the early follow up perıod

ord acute myocard al nfarct on early mob lıza arly exerc se tests rısk nd ca ors
Med Scand 206 169 1979

pt mal durat on of hospital zat on ın pat ents acute myocard al nfarct on (AMI) ıs not n S x weeks ın hosp tal was proposed ın 1955 l and Loeb (5) who based their recommen on the h stologıc study by Mallory et al (?1) showıng that ıt took some s x weeks for an nfarct to heal S nce then hosp tal zatıon t me has gradually decreased (9 ?0 30) and nowaday s 14–?1 da s are commonl\ recommended (?)

Levıne and Lown (18) ıntroduced earl\ armchaır treatment after a non complıcated AMI and Prınz metal et al (?8) advocated that pat ents w th m ld myocard al ınfarct on should be act vated early Several subsequent reports have shown that both early mob l zat on and early d scharge are possıble ın selected pat ents (1 1? 13 ?4 35 36) Boyle et al (4) and Chaturved et al (6) selected 6? and 40% respectıvely of the r pat ents for early d scharge b\ usıng rısk ınd cators (RI) based on ınformat on from the fırst seven days of the ıllness McNeer et al (?4 dıscharged after one week pat ents who had been w thout compl cat ons durıng the fırst four days No adverse effects from early mob l zat on and d s charge ın selected low rısk pat ents were reported ın any of these stud es

The best wa\ to select pat ents for rapıd mob l zat on and early d scharge ıs probably to assess the pat ents contınuously durıng theır hosp tal stay The a m of th s nvest gat on was 1) To evaluate the poss bıl ty of selectıng pat ents for rap d mob l zatıon (RM) and early d scharge usıng RIs both after 48 hours of treatment ın the Coronary Care Un t (CCU) and cont nuously durıng mob'l zatıon 2) To follow all pat ents for s x months ın order to evaluate the mob l zatıon schemes and RIs used 3) To evaluate the ınformat on from an exercıse test performed before d scharge ın RM pat ents

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Abb e a ons AMI acute myocard al nfarct on RI rısk nd cator CCU coronary care un t RM rap dly mob lızed rap d mob lıza on CM con en onally mo- b l zed convent onal mob lıza on LD lactate dehydro- genase CK creat ne phosphok nase

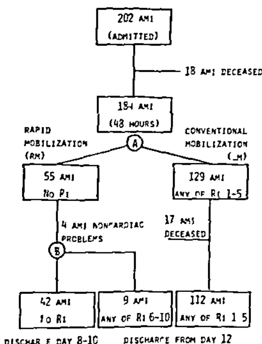


Fig 1 Schedule for admission mobilization and discharge of 202 AMI patients *A* = evaluation of early RIs after 48 hours treatment in the CCU *B* = evaluation of late RIs on days 3–8

METHODS

Criteria for admission diagnostic and therapeutic routines in the CCU and after-care unit have been given elsewhere (14)

We chose to evaluate electrical and mechanical dysfunctions of the heart after 48 hours treatment in the CCU by five RIs (early RIs) Patients without any RI at 48 hours formed the RM group and the remainder the conventionally mobilized (CM) group Enzyme values were determined twice a week in the after-care unit and 12 lead ECGs were recorded on days 3 5 and 7 No long term ECG monitoring was performed RM patients were transferred to the CM group if any one of five additional RIs was present during the mobilization (late RIs)

Five early RIs 1) A heart rate above 100/min or 2) a respiratory rate above 27/min for more than three hours were considered the two RIs indicative of left heart dysfunction 3) Maximum enzyme values either >36 μkat/l for heat stable lactate dehydrogenase (LD_1) or >18 μkat/l for creatine phosphokinase (CK) indicated a large infarct 4) Treated supraventricular and ventricular arrhythmias were considered to be RIs reflecting electrical instability Our treatment schedule in this respect is conventional but frequent monofocal multifocal or R-on T ventricular ectopic beats were not treated unless they recurred within one hour 5) Complete bundle branch blocks AV block II and III developing in the CCU also excluded a patient from the RM group

Five late RIs The RM group was continuously evaluated during mobilization and if one of the following RIs was present the patient was transferred to the C[illegible] 6) Signs or symptoms indicating reinfarction [illegible] gina or unstable ECG 7) Arrhythmias req[illegible] treatment 8) A systolic time interval index [illegible] >0 45 or 9) a chest X ray revealing pulmo[illegible] tion 10) A bicycle exercise test to a work load o[illegible] performed on the 7th day Two or more of the [illegible] findings during or after exercise excluded th[illegible] from the RM group heart rate exceeding [illegible] ST segment elevation or depression >1 m[illegible] arrhythmias requiring treatment and angina pe[illegible]

Mobilization and discharge All patients we[illegible] under guidance of a physiotherapist RM pa[illegible] allowed to sit from the third day onwards to [illegible] the ward from the fourth and were discharg[illegible] 8th–10th day In contrast the CM patients w[illegible] bed for 4–5 days whereafter they were allo[illegible] Walking around the ward was allowed from app[illegible] day nine and the patients were discharged [illegible] onwards The RM patients were seen as out-pa[illegible] week after discharge when a new exercise te[illegible] formed and systolic time intervals were eval[illegible] patients were thereafter seen six weeks th[illegible] months after discharge in the Out Patient Dep[illegible]

Statistics Conventional statistical methods [illegible] Differences between relative numbers were te[illegible] χ^2 test Yate s correction was applied

PATIENTS

During the one year study period 453 pa[illegible] mitted Myocardial infarction was diagnosed [illegible] tients 184 of whom survived the first 48 hou[illegible] Fifty five patients were free from RIs during [illegible] hours thus forming the RM group while [illegible] formed the CM group The age and sex distri[illegible] similar in both groups with a mean age of 6[illegible] male female ratio of 2 1 Nine RM patients [illegible] quently transferred to the CM group because [illegible] Four additional RM patients were excluded [illegible] non-cardiac disorders leaving 42 patients for [illegible] charge Of these 42 patients 39 could be [illegible] within 10 days (mean 9) The corresponding fi[illegible] patients was 19 days (range 12–36)

RESULTS

Early risk indicators and mortality

The six month mortality in relation to the [illegible] of positive early RIs is given in Table [illegible] mortality (5%) was found in patients with [illegible] early RI in the CM group against 39% in th[illegible] four or five RIs No RM patient died on di[illegible] in contrast to 17 in the CM group ($p<0.0$[illegible] of these 17 patients died in the CCU of [illegible] failure Ten patients died during after-care [illegible] cardiac rupture four of cardiac failure and [illegible] denly during sleep One patient in the R[illegible]

[3] *Mortality reinfarction and readmission for other reasons than AMI and recovery during six in relation to early and late RIs in RM and CM patients*

within parentheses indicate per cent

arly RIs	RM patients (n=42) 0	CM patients (n=138) 1	2	3	4–5	Any late RIs
y within 6 mo	1 (2)	2 (5)	10 (21)	9 (35)	7 (39)	1 (11)
tion within 6 mo	1 (2)	4 (11)	7 (15)	8 (31)	7 (39)	2 (22)
ssion due to other IHD	6 (14)	8 (21)	18 (38)	8 (31)	3 (17)	5 (56)
recovery	34 (81)	24 (63)	12 (26)	1 (4)	1 (6)	1 (11)
	42	38	47	26	18	9

patients in the CM group died of reinfarction ay 21 The difference in total mortality on -180 between the two groups is significant 1)

tality in relation to each RI is illustrated in The early RIs were associated with some different mortality patterns RIs 2 and 5 were t in 22 and 17% of the patients respectively RIs 1 3 and 4 were seen in 33 34 and 44% atients with RIs 2 and 5 showed a high early 21 days) mortality of 29 and 28% compared 17 and 12% for RIs 1 3 and 4 respectively 01)

e mortality in CM patients with only one RI was comparable to that in the RM group patients were studied separately (Table II) A prognosis was noted for the five patients with high enzymes only though definite con ns cannot be drawn because of the small num f patients

ation of late RIs

initial 55 RM patients five had been transfer the CM group due to the presence of late RIs the exercise test and another four were ex d because of non cardiac problems Accord 46 patients performed the exercise test on even Of these 46 patients 22 developed one developed two of the pathological parameters g the exercise test (Table III) thus excluding atter 4 patients from early discharge Three of four patients were later readmitted because of pain and reinfarction developed in one When sing the 26 patients with abnormal findings at ise (Table III) one of seven with a heart rate eding 125/min died within six months three arcted and three were readmitted for other IHD manifestations Of the 6 patients with angina at exercise three reinfarcted and two were readmitted for other IHD manifestations

Reinfarction and readmission

None of the RM patients had developed signs or symptoms suggesting any cardiac complications when examined one week after discharge Two per cent of the RM patients reinfarcted within six months against 20% of the CM patients ($p<0.01$) The frequency of reinfarction increased from 11% in patients with one early RI to 39% in patients with four or five RIs (Table I) Two of the nine patients transferred from the RM to the CM group devel oped a new infarct

Six (14%) of the RM patients were readmitted for other reasons than AMI (angina pectoris arrhyth mias congestive heart failure etc) (Table I) In patients with one or more early RIs the corre sponding figures were 17–38% Five (56%) of the nine patients with late RIs were readmitted during the six month follow up



Fig 2 Mortality for each early RI in 184 AMI patients between days 2 and 21 (▨) and between days 22 and 180 (□)

Table II *Mortality and IHD morbidity in 47 patients with one RI only during the six month f/u*
For RI 1–10 see text

	RI 1	RI 2	RI 3	RI 4	RI 5	Any RI 6-
Diseased	1	–	–	1	–	1
Reinfarction	1	1	–	1	1	2
Readmission for other IHD	2	2	–	2	2	5
Normal recovery	6	2	5	11	–	1
Total	10	5	5	15	3	9

Recovery and return to work

Of the RM patients 81% had a normal recovery compared to 29% of the CM patients (Table I) The RM patients were more often in active work prior to their AMI (69%) than CM patients (47%) RM patients resumed work both earlier and more frequently than CM patients (Fig 3) Thus among those working before the AMI 24% ($n=7$) of the RM patients and 5% of the CM patients had returned to work at three months The corresponding figures after six months were 66 and 25%

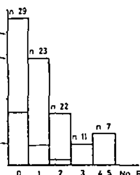
DISCUSSION

Most complications in AMI occur during the first 48 hours (15) They are however still frequent 2–3 weeks after an AMI (24 34) a fact that probably has prevented trials of rapid mobilization and early discharge (25) On the other hand immobilization per se has well known disadvantages e g thromboembolic episodes (22 27) muscle wasting and orthostatic intolerance (8) Rapid mobilization has not been found to increase the incidence of complications such as aneurysm formation or rupture in selected groups of AMI patients (11 12) Short periods of immobilization would therefore seem preferable in selected patients with a low risk of complications (13) Several studies have been presented regarding the feasibility of early mobilization and discharge in selected patients Most of these have been uncontrolled (4 24 28 37) but a few controlled studies have appeared (6 ... None of these investigations showed any ... effects of early mobilization and discharge ... seemed feasible and ethically justified to ... prospective clinical trial of early mobilization ... early discharge in patients with uncom... AMI No previous studies have been ... combining early selection of candidates for ... mobilization and early discharge

In order to select low risk patients we ... indicators both after 48 hours treatment and ... uously during mobilization The RIs were ... to exclude patients with severe mechanical ... electrical dysfunction of the heart from ... lization A heart rate above 100/min and a ... ry rate above 27/min have previously been ... ered good predictors for early as well as l... ity (4 13 14 16 24 36) CK and the therm... fraction of LD correspond fairly well with the ... of the myocardial necrosis (3 7 33) Our ... CK and LD_1 were based on the studies of ...

Table III *Findings during exercise test on the seventh day after AMI in relation to mortality, ... hospital treatment and recovery in 46 patients*

	Angina pectoris	Heart rate >125/min	ST deviation >1 mm	Arrhythmia
Mortality (days 22–180)	–	1	1	–
Reinfarction (days 22–180)	3	3	1	–
Hospital treatment for other IHD manifestation	2	3	3	1
Normal recovery	1	–	7	–
Total	6	7	12	1



Patients resuming work within three (□) and six □ n=Number of patients in active work prior to nd discharged from hospital *No RI*=number of ach patient

hardt (7) with the intention of excluding s within the upper third of the enzyme scale s who had high enzyme levels as their only wever proved to have a relatively low mor Obviously major structural damage does not arily lead to abnormal heart function and/or ed risk of complications Severe ventricular mias in the early phase of an AMI have been to be related to severe myocardial damage ge infarcts but also to be an independent or of future complications (26 29 31) Supricular arrhythmias are related both to age the presence of heart failure and may there so be related to an increased risk Patients traventricular as well as AV nodal conduc isturbances also have a high incidence of cations and a raised mortality during the ear valescence period (16 24) We made this in 32 of our patients and mortality during rst three weeks was approximately 30% is in agreement with previous findings (19) use of RIs in the evaluation of patients for g mobilization schemes has been different ts without RIs in our study had a very low nce of reinfarction during the follow up pe nd only one patient died Similarly few com ons were seen in patients with only one RI ting that RM could be extended also to these ts Hayes et al (13) mobilized their patients ling to an index score after 48 hours treatment U but the patients remained in hospital for days In contrast Boyle et al (4) and Chatur t al (6) used RIs based on all information available after the first six or seven days with the purpose of selecting patients to be discharged from day eight onwards

Applying a mobilization program as used in our study some 25% of the AMI patients may safely be discharged after 8–10 days This figure is low compared to 40–60% presented in other studies (4 6 24) On the other hand another 20% i e patients with one RI only had the same outcome but with CM The final decision about discharge in the RM group was made after an exercise test Exercise tests have previously been performed 2 3 weeks after an AMI (10 17) without apparent negative effects The 50 W work load resulted in a mean increase in heart rate from 72 to 103/min which is in agreement with the results of Ibsen et al (17) at the corresponding work loads in patients exercising three weeks after an AMI Excessive heart rates and angina pectoris during the test appeared to be sensitive parameters for later complications A light exercise corresponding to stair walking may also have reduced anxiety

The time of return to work is often used as a parameter to measure the success of rehabilitation schemes following AMI Several factors however will affect the time of resuming work and Winter and Kellerman (39) suggested that the socio-economic structure of different countries including the degree of unemployment is the basic determining factor Accordingly figures in unselected patient groups vary between 17 and 90% (38 39) six months post AMI which may be compared to 66 and 25% in the RM and CM groups in our study As the male/female ratio and mean age were similar in the RM and CM groups the difference probably reflects a higher pre AMI morbidity in the CM than in the RM group which in turn may increase the probability of developing complications As no control group is available in our study little may be concluded about a possible shortening of convalescence in the RM group Also we know little about the benefit—if any—of keeping the remaining patients i e those with RIs in hospital for longer periods

There are obvious economic benefits associated with early discharge of AMI patients (23) Our study indicates that 7–10 days of high-cost care could be saved for each RM patient which corresponds to total saving of some 400 hospital days/year in our hospital Possibly in the future low risk patients may spend an even shorter time in hospital and be

more rapidly mobilized than is the present routine The mobilization and discharge decisions must however always be made individually in order to minimize any risk involved to the patient

ACKNOWLEDGEMENT

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Arrhythmias in the Coronary Care Unit Recognized with the Aid of Automated ECG Monitoring

A T el e Month St d in 679 Pat ents

Johan Hulting

n Depa ment of Med c ne I Sodersj kl set Stockl olm and tl e Depa tment of Med cal Inforn at cs L nkop ng Un ers ty L nkop ng Sweden

ACT Arrhythmia incidence in 339 patients I 340 without proven acute myocardial in (AMI) has been compared with the aid of an ed arrhythmia monitoring system Seventeen s of arrhythmia could be made with the sys resulted in alarms All ECG write-outs were manually The patients were further divided classes of previous myocardial infarction evious or present heart diseases (HD) and no HD Except for atrial fibrillation or flutter dycardia all arrhythmias studied were sig y more common in patients with than with I Arrhythmia incidences in AMI/non AMI regarding paired ventricular ectopic beats tachycardia (heart rate >120/min) par supraventricular tachycardia (SVT) and an 5 VBs per min were 72/38 55/34 50/22 29% respectively Arrhythmia incidence in ous subclasses of AMI patients did not d ffer ly In the non AMI group most ventricular mias were less common in patients without e mortality in asystole ventricular fibrillation itricular tachycardia (VT) did not d ffer be AMI and non AMI patients Most other ven and supraventricular arrhythmias were as- with a poorer prognosis in AMI than in II patients No statistical d fference in out as observed between AMI patients with and VT In AMI paired VBs or SVT carried a gnosis during stay in the Coronary Care CU) The prognostic implications of several ias and poss bly the indications for antiar treatment in the CCU will be changed with monitoring methods

Is acute myocard al nfarct on arrhythm as co onary care un t mon toring prognos s

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years automated arrhythm a mon toring have gained widespread use in coronary s (CCUs) The majority of these systems are commerc al but despite several years of experi ence with such systems very few clin cal evalua tions have been presented so far An automated arrhythmia monitoring system has been developed in the CCU of Sodersjukhuset Stockholm The per formance of this system has been tested in long term rout ne monitoring (11 13) The mon toring system has been used in the present study to evaluate arrhythmia inc dence in the CCU The CCU and hospital mortal t es in d fferent ar rhythm as were also estimated

PATIENTS

A total of 850 card ac pat ents were adm tted to the CCU for automated ECG mon toring during a 12 month period end ng in April 1978 Excluded from the study were 157 pat ents w th unsuspected and non proven acute myocar d al infarct on (AMI) as well as 14 pat ents w th an uncer ta n or a long (>96 h) adm ss on delay def ned as the t me between onset of symptoms and start of mon toring Thus the study comprised 669 adm ss ons due to a suspected myocard al nfarct on (MI) and 10 pat ents w th AMI ad mitted for other reasons (ma nly pulmonary oedema)

During the 12 month period an add tional number of 86 pat ents were adm tted for ECG mon toring but observed n a general med cal intens ve care un t (ICU) located next to the CCU and run by the same personnel Reasons for ICU adm ss on were 1) impend ng or manifest resp ra tory fa lure 2) unconsc ousness follow ng resusc tat on and 3) all beds in the CCU occup ed Fourteen pat ents

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Abb e a ons AF atrial fibrillat on or flutter AMI acute myocard al infarct on AV atrioventricular CCU coronary care un t ECG = electrocard ogram elec trocard ograph c HD heart d sease HR heart rate ICU ntens ve care un t MI myocard al nfarct on RIR rap d d oventricular rhythm S-ALAT serum alan ne am notransferase S-ASAT serum aspartate aminotransferase S-LD serum lact c dehydrogenase SR s nus rhythm SVB supraventricular ectop c beat SVT paroxysmal supraventricular tachycard a VB = ventricular ectop c beat VF = ventricular fibrillat on VT ventricular tachycard a.

transferred from the ICU to the CCU were included in the results Forty two AMI patients not included were treated in the ICU with a mortality of 57%

Diagnostic groups

According to the final diagnosis the total patient material was divided into an AMI group (n=339) and a non AMI group (n=340) The groups were subdivided into the fol lowing classes *a*) previous MI *b*) previous or present heart disease (HD) without previous MI and *c*) no known HD prior to admission and as to the non AMI group HD unproven during CCU stay

Diagnostic criteria

The criteria for diagnosis of AMI were subjective symptoms leading to the suspicion and the development of pathological Q waves or R wave progression or two or more elevated serum aspartate aminotransferase (S-ASAT) values with a maximum 1-2 days after onset of symptoms and higher than a simultaneous serum alanine aminotransferase (S-ALAT) value or myocardial necrosis at autopsy corresponding in age to the onset of symptoms The isoenzymes of serum lactic dehydrogenase (S LD) were measured on the first and second day after admission and used as a diagnostic complement in patients with a long admission delay in whom the transferase values may have returned to normal A typical history of AMI with questionable S LD and aminotransferase values together with unspecific ECG changes e g ST wave changes was diagnosed as angina pectoris The diagnosis of previous MI was based on history hospital records ECG or autopsy Angina pectoris was considered in patients with typical symptoms for at least one month prior to admission

METHODS

The automated monitoring system

Eight patients could be monitored simultaneously on the automated monitoring system The system and the princi s for arrhythmia analysis have been described in great details elsewhere (28)

A total of 17 arrhythmia alarms and 7 alarms regarding the configuration of the ECG signal (monitoring status alarms) were reported by the system In the present study the definitions of arrhythmias in the computer program and in a subsequent manual interpretation were identical for most arrhythmias The alarm multiform VBs was excluded from the study because of difficulties in verifying this alarm from the short ECG strip available for interpretation The alarms were ranked and grouped into three priority levels When a particular arrhythmia event ful filled the criteria for more than one diagnosis the highest priority (ranking) condition was chosen by the computer A 2-channel Mingograph was activated at arrhythmia alarms One channel showed room number time of the event and the computer diagnosis the other a 5 sec re troactive ECG (paper speed 10 mm/sec) Usually this write-out had a duration of 15 sec *All write-outs were* collected and analysed off line by the author This in terpretation was made without any clinical information on the patients However in some patients in whom the single-channel ECG did not allow an accurate diagnosis the hospital records were studied in retrospect

Definition of arrhythmias

The principles of beat classification used [illegible] have been described earlier (11) Questionable beats were classified as supraventricular

The diagnoses of arrhythmias were made [illegible] sideration of the diagnostic message given by [illegible] puter except for the R-on T phenomenon [illegible] bigeminy and frequent ventricular or suprave[illegible] topic beats (VBs or SVBs) There was no [illegible] gorithm for the recognition of atrial fibrillation (AF) and AV block II-III All arrhythmias [illegible] two were ranked A special alarm missing [illegible] sensitive to abrupt changes in heart rate (HR) [illegible] in intermittent AV block II-III

The following arrhythmias were studied 1) [illegible] R R interval >5 0 sec 2) Ventricular fibrilla[illegible] irregular oscillating rhythm with a duration [illegible] absence of QRS complexes and atrial fibrilla[illegible] tricular tachycardia (VT) four or more VBs [illegible] with a rate of >120/min (VT_{120}) 4) Short or [illegible] three consecutive VBs with a rate of >100 [illegible] more than three VBs with a rate of 101 120 idioventricular rhythm (RIR) three or more [illegible] VBs with a rate of 51-100 6) Extreme brad[illegible] <35/min estimated over at least two consecu[illegible] tervals 7) Paired VBs two consecutive VBs [illegible] terval of <1 2 sec 8) Early VB VB falling on [illegible] of preceding ordinary beat 9) Ventricular bige[illegible] or more VBs alternating with normal be[illegible] Paroxysmal supraventricular tachycardia (S[illegible] or more consecutive SVBs with a rate of >1[illegible] sinus rhythm documented prior to or after the [illegible] mia episode 11) Frequent VBs more than 5 [illegible] 12) Frequent SVBs more than 5 SVBs [illegible] Tachycardia sinus or supraventricular rhyth[illegible] QRS rate of >120/min 14) Bradycardia [illegible] raventricular rhythm with a QRS rate of [illegible] 15) Second or third degree AV block absence [illegible] following a normal P wave 16) AF no P wa[illegible] irregular supraventricular rhythm with a length of [illegible] 20-30 SVBs A regular atrial flutter should be [illegible] a diagnostic ECG

The highest ranked arrhythmia in each [illegible] noted The delay between onset of monitoring [illegible] arrhythmia (arrhythmias 1-15) was estimated [illegible] to AF and AV block II-III only one diagnosis [illegible] from each write-out

The HR in ordinary supraventricular and [illegible] rhythm was obtained manually If four consecu[illegible] with a rate of >120/min occurred in a run of [illegible] episode was classified only as VT_{120} even [illegible] average rate of the arrhythmia episode was [illegible] The rate and length of all epidsodes of VT_{120} [illegible] each patient

In the terminal phase only the first episode of [illegible] VF or VT was noted A run of VT (more than [illegible] *complexes) passing into VF* was documented as [illegible] VF Arrhythmias were not studied during or [illegible] after resuscitation or during the implantation of [illegible] rary pacemaker An ordinary pacemaker [illegible] ignored

Uncertain interpretation concerning VT_{120} [illegible]

d as the number of episodes regarded as ventricu ıpraventricular in each patient Thus for VT_{120} hree levels of diagnostic accuracy were used in ıal interpretation 1) definite VT_{120} 2) probable ferred to the VT category and 3) questionable 'erred to the SVT category

-on T alarm was given by the computer system o VBs with the same shape and a short coupling had been detected by the system within 15 min er limit of this coupling interval was corrected for he QT interval limit for a HR of 60/min was set to *Early VBs were only studied when the corre* ; alarm had been reported by the automated sys

ıses of S ASAT and S ALAT AMI

ımum S-ASAT value sampled 18–48 h after the symptoms was used as a measure of the size of Only an S-ASAT value at least 100% above a eous S-ALAT value was approved The S ASAT hich begins to rise 8–10 h after the onset of ıs of AMI and reaches a maximum after 20–30 h ı used to estimate admission delay in a few pa ıth more than one peak of chest pain prior to ın

ıthmic treatment

countershock was utilized in VF and life threaten Lignocaine was used as the drug of first choice in lar arrhythmia during the first 48 h after onset of ıs and when a rapid effect was desired Lig was usually withheld until VT_{120} or VF had been :d *It was administered according to a restrictive* s a bolus (75–100 mg i v) followed by a continu sion for at least 12 h at a rate of 1–3 mg/min Oral ımide quinidine and disopyramide were some ıen against recurring ventricular arrhythmias but n prophylaxis after VT or VF in the acute stage given routinely

lis was usually omitted on admission but diuretics en liberally if signs of cardiac failure were pres- rapid AF (HR>130) or in frequent SVT vera as usually tried first unless signs of heart failure ident In such cases digoxin was given Digoxin o added to the regimen of patients with heart fail- responding satisfactorily to several days of treat ith high doses of frusemide

mptomatic bradycardia atropin was first attempt ents with total block bradycardia and signs of low output were usually given an infusion of iso- l but if this regimen failed a transvenous ker electrode was passed via the subclavian vein on β-blocking agents before admission were sly given this medication in the CCU unless indications were apparent β blockers were given to patients with unstable angina pectoris but not ly as antiarrhythmic agents

s

ion regarding sex age admission delay mon time in the CCU previous treatment (digitalis diuretics β blockers) and outcome was punched on cards together with data concerning diagnoses arrhythmias enzyme values etc for further analysis with a general computer

Student s t test and the χ^2 test (four field table two-tailed test) with Yates correction were used for the evaluation of statistical significances of means and relative numbers respectively at the 5 1 and 0 1% level The exact test was used if the expected number in the four field table was 5 or less All tests of significance were performed on a Texas Instruments calculator (*SR 52*) *The term significant used below refers to a probability of* $p<0.05$

RESULTS

General characteristics of the diagnostic groups (Table I)

The mean age in the AMI group was 66 years and 63 years in the non AMI group AMI patients with HD were older and those without HD were younger than the rest Non AMI patients without HD had a mean age more than 10 years below that of the others The proportion of women with AMI was *higher in cases with previous HD except MI The* proportion of AMI patients with an admission delay of ≤12 h was greater among patients with previous MI

The prevalence of angina pectoris and hyperten sion did not differ between AMI and non AMI pa *tients A history of cardiac failure was more com* mon in non AMI patients as well as treatment with digitalis and diuretics

The CCU and total hospital mortalities from AMI were 16 and 21% respectively These figures were significantly higher than the corresponding values *(2 and 6%) in the non AMI group* However the mortality among AMI and non AMI patients with out previous HD was not significantly different AMI patients with previous MI had a higher mor tality than the rest and the total hospital mortality was lower (12%) among AMI patients without pre vious HD

The average size of the MI evaluated from maximum S-ASAT was larger in patients without previous HD and smaller in those with acute rein farction

Arrhythmias in the various diagnostic groups

All but two arrhythmias viz bradycardia and AF on admission were more common in the AMI than in the non AMI group (Table II) In patients with previous MI the incidence of VF and AV block

Table I *Some clinical and laboratory data on 679 patients with proven or non proven AMI*

	AMI total (n=339)	AMI with previous MI (n=95)	AMI with previous HD except MI (n=150)	AMI without previous HD (n=94)
Age (y)[a]	66±9*	67±7	68±**	63±10 *
Monitoring time (h)[a]	72±36***	73±38***	71±38***	72±37**
Sex ratio (♂/♀)	2 2	4 6*	1 1***	3 7*
Admission delay ≤12 h (%)	79	89**	69***	83
Previous angina pectoris (%)	46	58	68*****	0
Previous hypertension (%)	32	26	56****	0
Previous cardiac failure (%)	11	19**	13	0
Previous diabetes mellitus (%)	10	10	11	10*
Digitalis on admission (%)	27	51***	26	4
Diuretics on admission (%)	30	44**	39	1
β blocker on admission (%)	17	17	26***	1
CCU mortality (%)	16***	23****	15***	11
Total hospital mortality (%)	21***	31***	21***	12*
S ASAT $_{max}$ (μkat/l)	3 8±2 6	3 2±2 2*	3 8±2 5	4 4±2 9*

[a] Mean ± S D

Statistical significance at the 5 1 and 0 1% level is indicated by * ** and *** respectively Upper position indicates that statistical analyses were performed between corresponding groups (classes) of patients with and without ... Lower position of asterisks indicates that statistical analyses were performed between one subclass of patients of AMI and non AMI patients respectively

II–III was not significantly different between those with and without AMI (Figs 1 and 2) In patients with previous HD except MI, AMI was associated with a significantly higher incidence of AF appearing after admission whereas the incidence of VF R on T VBs and ventricular bigeminy did not ... between patients with and without AMI (... and 2)

There were relatively small differences ... rhythmia incidence between the various di...

Table II *Arrhythmia incidence estimated from analysis of computer generated alarm write-outs ... CCU patients and mortality related to arrhythmia incidence*

	Arrhythmia incidence (%)		Mortality (%)			
			AMI		Non AMI	
	AMI (n=339)	Non AMI (n=340)	CCU	Total hospital	CCU	Total hospital
Asystole	7**	2	83***	83***	83***	83*
VF	6*	2	42**	47**	50	50
VT_{120}	38***	10	20	26	9	17
VT_{100}	43***	14	14	20	4	11
RIR	33***	7	15	19	0	4
Extreme bradycardia	11	6	61******	61******	5	5
Paired VBs	72***	38	13***	18*	3	9
R-on T VBs	15**	7	8	13	0	0
Ventricular bigeminy	31**	20	13**	19	0	7
SVT	50***	22	10***	17**	1	1
More than 5 VBs/min	49***	29	18***	24**	1	8
More than 5 SVBs/min	45***	28	16**	24**	3	9
Bradycardia	39	45	16**	19***	4	5
Tachycardia	55***	34	20**	28*****	6**	10
AV block II–III	12***	4	36**	43***	7	13
AF (on admission)	13	15	28*	42*****	6	10
AF (SR on admission)	9***	3	20	23	0	11

Symbols and statistical analyses as in Table I Lower position of asterisks indicates that statistical analyses ... performed between patients with and without arrhythmias in the two diagnostic groups

...ith previous	Non AMI without previous or present HD
HD except MI (*n*=150)	(*n*=49)
64±10	53±8***
43+31	30±18*
1 6	2 5
71	73
49	0
38 *	0
19	0
12	0
38	0
35	2
20	4
2	2
5	2

...in AMI (Figs 1 and 2) Bradycardia ex...
...radycardia and frequent VBs were more
... in patients with a history of MI Most
...lar arrhythmias were less common in pa...
...ith previous HD except MI but the differ...
...ere not statistically significant (Fig 1)

In the non AMI group patients without previous or present HD had a significantly lower incidence of VT paired VBs R on T VBs ventricular bigeminy SVT and frequent VBs than those with HD (Figs 1 and 2) All ventricular arrhythmias were more common in patients with previous MI than in those suffering from other HD even though the possible statistical significance was not tested

As to the ventricular arrhythmias the proportion of patients whose arrhythmias occurred during the first 12 h of monitoring ranged from 0 65 to 0 77 (Table III) Somewhat lower figures were usually found in the non AMI group The proportion of patients with extreme bradycardia and more than 5 SVBs/min occurring during the first 12 h was relatively low (<0 40) and essentially similar in AMI and non AMI patients

Of patients with asystole VF or AV block II–III 10–67% had their first arrhythmia episode in the last hour of monitoring (Table III) Such arrhythmias were always fatal In the AMI group extreme bradycardia also belonged to arrhythmias often recorded terminally

Hospital prognosis in the arrhythmias studied (Table II)

The mortality among patients with asystole was about 80% and among those with VF about 50%

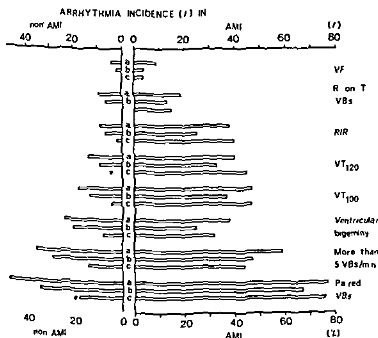


Fig 1 Incidence of ventricular arrhythmias in subclasses of patients with proven and non proven AMI *a* History of previous MI *b*=history of previous HD except MI *c* no previous or present HD Statistical analyses at the 5 (★) 1 (★★) and 0 1% (★★★) level performed between one subclass of patients within each arrhythmia group and the rest of AMI and non AMI patients respectively

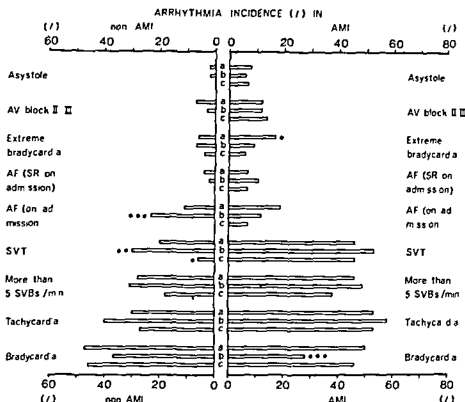


Fig. 2 Inciden... studied arrhyth... classes of pat... proven and no... AMI Symbols... analyses as in...

and no difference was observed between patients with and without AMI Regarding VT_{120} VT_{100} RIR R-on T VBs AV block II–III and AF appearing after admission there was no significant difference in mortality between AMI and non AMI patients even though the absolute values were higher the AMI group The other arrhythmias studied were associated with a higher CC... among AMI than non AMI patients

In the AMI group the CCU mortalit... among patients with asystole V... bradycardia tachycardia and AV bloc... among those without these arrhythmia... total hospital mortality was considered...

Table III Proportion of arrhythmias occurring during the initial 12 hours of monitoring and... last hour of monitoring

	Arrhythmia during first 12 h		Arrhythmia during last h	
	AMI	non AMI	AMI	non AMI
Asystole	0 48	0 67	0 43	0 67
VF	0 68	0 63	0 11	0 13
VT_{120}	0 67	0 56	0 02	0 00
VT_{100}	0 66	0 57	0 01	0 02
RIR	0 72	0 58	0 01	0 04
Extreme bradycardia	0 33	0 29	0 19	0 05
Paired VBs	0 77	0 74	0 01	0 03
R-on T VBs	0 65	0 60	0 00	0 04
Ventricular bigeminy	0 69	0 60	0 02	0 03
SVT	0 46	0 53	0 01	0 01
More than 5 VBs/min	0 76	0 77	0 00	0 03
More than 5 SVBs/min	0 39	0 37	0 03	0 03
Bradycardia	0 74	0 70	0 05	0 00
Tachycardia	0 54	0 71	0 02	0 03
AV block II–III	0 41	0 80	0 12	0 15

also turned out to be an ominous sign The ortality in AMI was significantly lower patients with paired VBs and SVT The lat ing was however not confirmed when the spital mortality was considered No differ *mortality was observed between AMI pa* ith or without VT_1 ,
ng the non AMI patients only those with paired VBs or tachycardia had an in l mortality compared to the rest

DISCUSSION

alysis of arrhythmia incidence in the CCU primary purpose of this study The prog implications of various arrhythmias were as a secondary goal
Total monitoring time for the 679 patients was h However the ECGs from all 850 patients monitoring hours) had to be analysed since rutiny of write-outs was performed without information on the patients A manual y beat analysis of a slow speed paper record m all patients would be very time consuming the application of the automated system was advantage To my knowledge the capacity of system has not previously been utilized in I research Computer assisted analysis of ECG material could be used in a study of the t type but data collection and analysis would y laborious
application of the monitoring system seemed ited in view of results from a previous evalua 2) showing that about 90% of patients with ventricular and supraventricular arrhythmias ecognized after scrutiny of alarm write outs ming VT_{120} 79% of mixed CCU patients his arrhythmia were identified and all patients asystole and VF had at least one of these les reproduced on the write outs (11) How the number of patients with the last mentioned thmias was small
arrhythmia incidence among a large number AMI patients has not been presented earlier nsen (27) analysed arrhythmia incidence dur e first 24 h the CCU using a continuous ECG ding for arrhythmia documentation He ap a restrictive policy for the administration of aine and observed VT (2 or more VBs with a f >100) in 65% of 37 AMI and in 12% of 43 AMI patients For frequent VBs (more than 5/min) consecutive VBs (2 or more in succession) and R on T VBs his corresponding figures in the two diagnostic groups were 62 and 19% 81 and 28% and 59 and 2% respectively Apart from the high incidence of R on T VBs these figures were *only slightly higher in the AMI* group and some what lower in the non AMI group compared to the present findings R on T VBs were analysed in the present study only at this alarm which partly explains the relatively low incidence of this ar rhythmia

The majority of patients with arrhythmias in the AMI and non AMI groups had their first arrhythmia within the first 12 h of monitoring (Table III) Thus the longer monitoring time in AMI patients (Table I) probably did not contribute markedly to the higher arrhythmia incidence in AMI compared to non AMI patients

A short admission delay of AMI patients and extensive infarction are associated with a higher incidence of ventricular arrhythmias (4 26) AMI patients with previous MI had a shorter admission delay but smaller infarctions on the average Thus the influences of these factors on arrhythmia inci dence might have cancelled out each other AMI patients with previous HD had a higher mean age lower male female quotient longer admission de lay higher incidence of previous angina pectoris and hypertension and used β blockers more fre quently than the rest of the AMI patients One or more of these findings could possibly explain the slightly lower incidence of most ventricular ar rhythmias observed in AMI patients with previous HD except MI (Fig 1)

The incidence of cardiac arrhythmias in AMI has been reported in a great number of publications in *the last 15 years (1 10 15 16 19 23 25 26 31 32* 33 38 40) Several factors such as selection of patients definition of arrhythmias admission de lay principles for antiarrhythmic treatment may influence arrhythmia incidence in the CCU The length of and methods for arrhythmia monitoring have varied The above circumstances complicate a comparison between the earlier and the present re sults Below however some findings will be dis cussed and related to earlier results in AMI pa tients

Asystole Ten of 23 cases with asystole (R R >5 0 sec) in the present study had their first asystole episode within one hour prior to death Four out of the other 13 patients survived their stay in hospital

Table IV *Ventricular tachycardia in AMI during CCU stay reported in some studies*

	Principal method for arrhythmia documentation	Studied period of CCU stay	Maximal admission delay (h)	No of cases	[illegible]
Spann et al (38)	Arrhythmia detector	Total	30	30	[illegible]
Julian et al (16)	Oscilloscope monitoring	Total	48	100	11
Lown et al (23)	Oscilloscope monitoring	Total		300	13
Bashour et al (1)	Taped ECG avionics system	First 24 h	18	30	
Dalle et al (5)	Oscilloscope monitoring + R R detector	First 96 h		300	
Mogensen (26)	Oscilloscope monitoring	Total		421	10
Mogensen (26)	Continuous ECG recording	First 24 h		37	
de Soyza et al (37)	Taped ECG avionics system	First 24 h	24	52	
Henning & Lundman (10)	Oscilloscope monitoring	First day in CCU		1 831	16
Löfmark & Orinius (24)	Oscilloscope monitoring	Total		274	[illegible]
Present study	Computer-generated alarm write-outs	Total	96	339*	15

* Patients with shock higher degrees of AV block and abundant supraventricular arrhythmias were exclu...
* Patients with an uncertain admission delay were excluded

Asystole (R R >3 0 sec) and excluding terminal ents have been reported in 7% of AMI patients a total hospital mortality of 75% (26)

Ventricular fibrillation Transient self terminating forms of VF were observed in one AMI and two non-AMI patients Such episodes constituted 5 and 25% of first VF in AMI and non AMI patients respectively The incidence of VF in the present material (6%) lies near the middle of the incidence (1–16%) reported earlier in AMI (16 17, 20 23 25 26 31 32 40)

Five out of 19 patients had their first VF episode without earlier signs of heart failure or hypotension (primary VF) The first VF only rarely ended fatally (Table III) Six patients with later proven AMI were defibrillated before arrival at the CCU Four out of these 6 episodes of VF were considered primary If these 6 cases were added to those previously reported the total hospital mortality in primary VF secondary VF and all VF was 11 56 and 40% respectively These figures are somewhat lower than those reported by Lawrie et al (Mogensen (26) Two non AMI patients had ... clusively before admission both ... hospital stay

Ventricular tachycardia The incidence ... the present and some earlier studies is ... Table IV In 1967 Lown et al (23) prese... dence for the value of lignocaine in so-call... ing arrhythmias (runs of VBs R-on-T V... frequent or multiform VBs) in AMI This ... of treatment given in order to prevent V... generally accepted and practised in ... (10 23 large series 26) As a prophylact... lignocaine reduces the incidence of VT in ... 30) the indications for antiarrhythmic ... must also be considered when comparing ... Table IV In two studies (24 small series ... nocaine was given only when VT or post ... detected However even though many fac... influence the incidence of VT the high fr... served for runs of VBs (VT) in the prese...

tachycardia

Rate above (min ⁻¹)	Incidence (%)	CCU mortality (%)
100	37	27
	6	67
70	28	20
99	50	
100	18	47
50	40	16
100	65	
100	52	
100	30	30
50	41	
50	65	21
100	57	21
120	38	26

ly reflect a high sensitivity of the automated ring system to this arrhythmia

ral previous studies have indicated that VT erunner of serious complications in AMI (5 19 24 26 31 40) This observation was not ned in the present series despite stricter a for the definition of $VT_{1\ 0}$ compared to used by most other authors In fact in the it study only AMI patients with 8 or more n succession with a rate of >120/min had a CCU and total hospital prognosis (p<0 01) hose with no or other runs of VBs It is con le that short and single episodes of VT were overlooked in previous studies whereas runs with higher rates carrying a poorer osis were detected As pointed out by Stock (40) an improved quality of arrhythmia oring will influence the prognostic value of d other arrhythmias

er ventricular arrhythmias RIR was ob- in 33% of the present AMI patients Other rs (34 37 38 41), using slightly different diagnostic criteria reported this arrhythmia in 13–36% of their patients The benign character of RIR has also been documented earlier (34)

Paired VBs was the most common arrhythmia in AMI in this study and the incidence of 72% certainly is one of the highest observed Paired VBs turned out to be a favourable prognostic sign in AMI and patients with this arrhythmia had a significantly better CCU prognosis than those without A similar observation was made by Julian et al (16) who found that patients with a low number of VBs during the CCU stay had a better prognosis than those without VBs

R-on T VBs were recorded in 15% of the present AMI patients compared to 2–9% of patients monitored on oscilloscopes (16 19 26 31) and to 10–49% of patients whose ECGs were taped and analysed off line (1 6)

In some previous studies the majority of ventricular arrhythmias (paired VBs R-on T VBs and frequent VBs) were associated with an increased mortality (16 19 26) This observation was not confirmed in the present study probably due to an increased detection rate of relatively benign arrhythmias

Supraventricular tachyarrhythmias Other authors report an incidence of 33–50% in tachycardia (sinus or supraventricular rhythm with a rate of >100/min) with a hospital mortality of 28–52% (15 16 26) An even higher incidence (55%) was found in the present series despite a stricter definition (HR>120/min) and the poorer prognosis for these patients was confirmed However the relationship between increased mortality and the presence of tachycardia did not persist if patients with AF and tachycardia were excluded from all cases with tachycardia

SVT or atrial tachycardia has been reported at a rate of 2–11% (15 16 19 23 25 26) but no clear diagnostic criteria were given In two series SVT was defined as three or more consecutive SVBs with a rate of >100/min and was found in 4% with the use of conventional monitoring (22) and in 29% from continuous ECG recording (21) In the latter report patients with AF were excluded and the same procedure reduced the SVT rate from 50 to 37% in the present material Thus it appears that the monitoring methods used by most previous investigators were insensitive to short runs of SVBs but different diagnostic criteria could also contribute to the low incidence of SVT

reported in some series The benign character of this arrhythmia has been recognized earlier (22 23) In the present series patients with SVT had a significantly better CCU prognosis than those without However this effect did not remain significant when the total hospital mortality was considered even after exclusion of patients with concomitant AF

Atrial fibrillation and flutter were not separated in the present study for two reasons Firstly a differentiation from a single lead recording may be impossible secondly transitional forms are common The incidence of AF in this study as well as the poorer prognosis for patients with this arrhythmia compared to those with SR are in line with earlier results (3 9 14 18, 22 39) However the better prognosis for patients developing AF compared to those with AF on admission has not been stressed earlier

Bradyarrhythmias (AV block II–III) Bradycardia was observed in 39% of the present AMI patients In this group no significant relationship was observed between the occurrence of bradycardia and treatment with digitalis or β blockers prior to or during the CCU stay In the non AMI group *bradycardia was the most common arrhythmia* (45% of all cases) Bradycardia (supraventricular rhythm <50/min) has been noted by other investigators with a frequency of 11 and 21% (25, 26) No figures regarding the incidence of bradycardia in non AMI patients have been reported earlier

Conflicting results regarding the prognostic im of bradycardia have been reported with a higher (26) or a lower (15 19 23) mortality rate than average among patients with AMI In the present study a HR of 35–50/min was not related to an increased risk for the patient whereas extreme bradycardia (HR <35/min) was an ominous sign in AMI but as to outcome of little importance in non AMI patients In the latter group extreme bradycardia was noted in 21 cases in 16 in association with extreme supraventricular bradycardia (slow SR atrial or nodal origin) with a 6% mortality and in 5 cases in association with AV block II–III with a 20% mortality Extreme bradycardia was noted in 36 AMI patients in 13 associated with extreme supraventricular bradycardia (mortality 38%) in 15 with higher degrees of AV block (mortality 47%) and in 8 with an idioventricular rhythm with no or an irregular atrial activity (mortality 100%) Thus the very slow rhythms irrespective of type carried a poorer prognosis in AM non AMI patients although the rel number of patients did not permit an accu tical analysis Slow supraventricular arr non AMI patients were relatively ben proportion of terminal bradyarrhythmias partly explained the very high mortality bradycardia in this patient group

Lignocaine treatment In the present nocaine by infusion was given to 21% of 2% *of non AMI patients* whereas abo 50% respectively fulfilled the criteria Lown et al (23) for prophylactic trea lignocaine VF and $VT_{1\,0}$ were diagnosed 70% respectively of AMI patients tre lignocaine VT_{120} was found in 30% of AM not receiving this drug and in 81% of the only one episode of $VT_{1\,0}$ was documen write-outs contrasting with 27% of tients The restrictive use of lignoca obvious negative influence on the out probably influenced the incidence of VT to a minor degree only A few patients only the bolus dose of lignocaine but the patients for whom this drug was cons *necessary or contraindicated* was not re more restrictive use of antiarrhythmic dr justified with efficient ECG monitoring (7) recently suggested general ligno phylaxis in AMI partly due to a relatively ciency of conventional ECG monitoring

Uncertain interpretation regarding VT ent study was noted specifically Base information minimum and maximum val incidence of VT could be calculated tients the minimum value for VT_{120} was maximum 41% and for VT_{100} 40 and 45% tively In the non AMI group the corre figures for $VT_{1\,0}$ were 9 and 12% and for and 14% Thus questionable VTs were rather few patients and a *change in the* policy concerning questionable beats have influenced markedly the incidence of

Apart from arrhythmias other circum fluence the prognosis during the stay Some factors adversely affecting the AMI are high age (8 10) bundle bran 26 40) heart failure (17 35) cardi (29) and extensive myocardial dama these factors showed significant relati several of the arrhythmias studied

sent study the prognosis has been estı ter a qualitat ve analysıs of arrh thm as A at on of arrhythmias and an estimation of s in various combinations of arrhythm as is Also arrhythmias preceding the most events should be studied The h gh inci of ventricular and supraventricular ar as in AMI was confirmed and compared to a material of nearly equal size The prog implicat ons regarding the arrhythmias probably val d for CCUs w th eff cient nitoring

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Intraaortic Balloon Pumping in the Treatment of Cardiogenic Shock Complicating Acute Myocardial Infarction

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ACT A 5 1% incidence of cardiogenic shock
id in a consecutive series of 680 patients with
yocardial infarction (AMI) during a five year
The hospital mortality was 94% Shock was
according to a stepwise policy including as
rculation with intraaortic balloon pumping
During the five-year period, only five pa
4% of the shock patients, had shock for more
ee hours (the minimal time for attempting
therapy and preparing for assisted circula
ere below 75 years of age and without ter
iseases Together with ten AMI patients in
eferred from or treated in other hospitals,
er 15 patients were given IABP during 1–318
nean 58) Shock was reversed in 12 (80%) of
atients and five (33%) could be weaned off
nd discharged from the CCU However, only
ients (13%) *were long term survivors*

ds acute myocardial infarction intraaortic bal
mping assisted circulation cardiogenic shock—
n—treatment—mortality
'd Scand 206 189 1979

complicating acute myocardial infarction
still accounts for a major proportion of the
l mortality of AMI Much effort has there
en made to reduce the mortality of car
c shock during *recent years especially by*
of mechanical circulatory support The pres
port describes cardiogenic shock and as
irculation in a consecutive series of patients
MI seen in the coronary care unit (CCU)
a five year period

PATIENTS AND METHODS

'y population consists of (A) all patients with AMI
l to the CCU from Sept 1972 to Sept 1977 (B)
with cardiogenic shock secondary to AMI referred from other hospitals for assisted circulation (C) patients with shock and AMI treated with assisted circulation in another hospital during the period Dec 1970 to Dec 1971 The criteria for the diagnosis of AMI were 1) 2) and 3) below together with typical symptoms

1) *Appearance of a pathological* Q wave *and/or appear*ance or disappearance of a localized ST elevation followed by a T inversion in two or more of the 12 ECG leads 2) Two s ASAT values of 0 67 μkat/l or more and with a maximum about 24 hours after onset of symptoms in combination with lower s ALAT values 3) Autopsy findings of myocardial necrosis of an age corresponding *to the onset of symptoms*

Shock was defined as a palpatory systolic BP below 90 mmHg for more than half an hour in association with at least three of the following findings

1) Signs of reduced cerebral circulation such as mental confusion or unconsciousness 2) Signs of reduced peripheral circulation such as cold skin 3) Signs of impaired renal circulation with a urine flow of less than 20 ml/hour 4) Peripheral or general cyanosis 5) Metabolic acidosis

Patients fulfilling the above criteria of shock were treated according to the following stepwise policy

1) Correction of arrhythmias 2) A slightly head-down posture (except for cases of frank pulmonary oedema) 3) Oxygen 10 l/min by mask or nasopharyngeal catheter 4) Methyl scopolamine i v when the heart rate was below 80/min 5) Correction of acidosis 6) Rapid infusion of 300 ml 5 5% glucose if frank pulmonary oedema or signs of elevated central venous pressure were not present 7) Assisted circulation to patients below 75 years of age without other disabling or terminal diseases

Assisted circulation was performed by means of intraaortic balloon pumping (IABP) The AVCO system with a three segmental balloon was used in patient groups A and B (defined above) and a monosegmented balloon and the Milton Roy Company driving unit in the patients of group C The balloon catheter was inserted into the femoral artery bedside in the CCU after local anaesthesia Inflation and deflation of the balloon were adjusted ac

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Abbreviations AMI = acute myocardial infarction IABP = intraaortic balloon pumping CCU = coronary care unit

Table I *Patients with cardiogenic shock secondary to AMI treated with IABP*

A=anterior L=lateral I=inferior VSD=ventricular septal defect AA=aortic aneurysm X=in shock o

Case no	Age (y)	Previous myocardial infarction	ECG site of AMI	Hours from onset of symptoms to shock	Hours in shock	Hours from shock to start of IABP	Hours of IABP	Shock disappeared	Termination of IABP/ CCU survival	h [illegible]
Group A										
1	54	–	A L	49	15	12	36	–	+	+
2	70	–	A L I	10	11	6	318	+	–	–
3	70	+	A	48	26	8	58	+	+	–
4	73	–	I L	12	15	4	11	–	–	–
5	58	–	A	1	5	4	28	+	+	–
Group B										
6	70	+	A L, I	X	9	8	1	–	–	
7	60	–	A L, I	X	14	10	19	+	–	
8	60	–	A L	X	27	15	12	–	–	
9	71	+	A L	X	10	7	10	+	–	
10	60	+	A L, I	X	70	7	85	+	–	
Group C										
11	74	+	I L	X	21	5	68	+	–	–
12	71	+	I	67	23	3	90	+	+	–
13	59	–	I L	X	37	2	41	+	–	–
14	67	+	A	X	8	3	17	+	–	–
15	58	–	I L	5	12	1	80	+	–	–

cording to the aortic pressure curve Details of the techniques have been described elsewhere (4)

Conventional statistical methods have been used for calculation of the arithmetic mean and standard deviation Significance of differences between mean values was tested by Student s *t*-test

RESULTS

Group A

During the five year period Sept 1972–Sept 1977 680 consecutive patients with AMI were admitted to the CCU (Fig 1) Fourteen (2 1%) were in shock already on admission and 21 (3 1%) developed shock later during their CCU stay In all 35 patients (5 1%) with a mean age of 70 years were in shock The mean age of the 645 patients without shock was 67 years The difference is not statistically significant.

Sixty per cent of the shock patients developed shock 1–96 hours (mean 22) after admission to the CCU The shock lasted for 1–37 hours (mean 8) for less than 3 hours in 15 patients One of these 15 patients had a rapid atrial fibrillation Shock symptoms disappeared after electroconversion and the patient was discharged alive from hospital

The other 14 patients died in shock. [illegible] tients who had shock for more than 3 h[illegible] more than 75 years old Shock sym[illegible] peared after electroconversion of [illegible] tachycardia in one of them but the pa[illegible] denly six days later

Five of the eight patients aged 75 or [illegible] shock for more than 3 hours receive[illegible] culation with IABP (Table I) The o[illegible] tients who were not treated with as[illegible] tion due to other terminal disease [illegible]

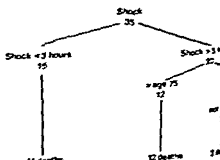


Fig 1 Outcome after treatment of cardiog[illegible] association with AMI in 35 shock patients du[illegible] year period

3P

hock d sappeared

IBP terminated
scharged from CCU

ng term survivors

utcome in 15 patients with shock complicating
ited with IABP

hock The time from onset of shock to start
ABP was 4–12 hours (mean 7) IABP was
r 11–318 hours (mean 90) In four of the five
shock symptoms disappeared during the
circulation One patient in whom shock
ns remained throughout the IABP period
rge aortic aneurysm at autopsy Three pa
ould be weaned off IABP The balloon
was extracted and they were all discharged
CCU Two of them died from reinfarction
19 days respectively after termination of
sted circulation The third patient was dis
from hospital and returned to work He
m reinfarction 3 years and 8 months later
tent (no 2) was completely pump depend
had a ventricular septal defect which the
declined to operate upon and died after
rs of assisted circulation

e 35 shock patients 14 had complete AV
nd/or periods of asystole during the shock
All died despite of transvenous pacemaker
nt The survival time in shock for these 14
varied between 1–37 hours (mean 9) One
was also treated with IABP

patients had physical signs of ventricular
lefect confirmed at autopsy in all

31 (89%) of the 35 shock patients died in
U The hospital mortality was 94% and only
tients could be discharged alive one after
nd one after cardioversion of atrial fibrilla

B

r eight patients with cardiogenic shock due
I were referred from other hospitals for as
irculation They were all in deep cardiogenic
on admission and had been given various
of drugs including *inotropic agents* Three
died before IABP could be started Five patients were treated with IABP for 1–85 hours (mean 25) (Table I) Shock symptoms disappeared in three but they all died in the CCU

Group C

Five patients with shock due to AMI were given IABP in the CCU of the Serafimer Hospital during a one year period 1970–71 (Table I) Assisted circulation was given during 17–90 hours (mean 59)

Shock was reversed in all patients during IABP which was terminated in two who could later be discharged from the CCU One of these patients died from reinfarction outside hospital after four years

Extensive myocardial necroses of varying ages were found in all autopsied shock patients

DISCUSSION

The incidence of cardiogenic shock in association with AMI was reported to be about 20% in the beginning of the CCU era Considerably lower rates 4–8% have been found by others (3) In the present consecutive series there was a 5% incidence of cardiogenic shock during a five year period Several explanations may be found for this reduced incidence among others a change of the criteria for cardiogenic shock Binder et al (1) reported on the inverse relationship between incidence and mortality rate of shock i e the lower the incidence the higher the mortality Another explanation may be a prevention of shock by better treatment of congestive heart failure arrhythmias fluid deficits and metabolic derangements

In the present series 14 of the 35 patients had terminal shock that is for less than three hours prior to death Thus the incidence of non terminal shock was 3% and more than half of the non terminal shock patients were above 75 years of age

In the present study the age of 75 years was regarded as a cut off age beyond which the patient was not considered for assisted circulation If three hours are the assumed minimal time required for attempting medical therapy and preparing assisted circulation only eight patients of the present consecutive five year series were candidates for assisted circulation

The IABP was very effective in reversing the shock state—reversed in four of five patients (the *fifth had a large aortic aneurysm) Among the 30*

patients not given IABP shock was reversed in only two—after electroconversion of rapid arrhythmias in both

Altogether 15 patients were treated with IABP (Fig. 2) In 12 (80%) of these shock was reversed and five (33%) could be weaned off assisted circulation and discharged from the CCU However only two patients (13%) were long term survivors These figures are in accordance with those reported by others (2) Although effective in treating the cardiogenic shock state IABP seems not to have changed the poor prognosis of shock in association with AMI

Autopsy revealed extensive acute and old myocardial damage in all IABP treated and other shock patients It is unlikely that any treatment medical or surgical could have saved these patients The only way may probably be to start IABP as early as possible preferably before shock develops

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Q Waves and Coronary Artery Disease

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Fr Med cal Depa tme t B R ssl osp alet C penl a en D n k

CT In a consecutive series of 234 patients – for selective coronary arteriography 78 t/olog cal Q waves In 32 of these 78 patients rowed left ventricular hypertrophy QRS of ≥0 12 sec incomplete left bundle branch left axis deviation Fourteen (44 %) of these ts had coronary artery disease (CAD) wh le of the remaining 46 patients without these inges had CAD ($p<0\ 0005$) Among the 46 34 of 35 with angina pectoris had CAD d to 6 of 11 without angina pectoris ($p<$ ur study thus shows that Q waves may be predictors of CAD especially in patients with ectoris

ls acute myocard al infarct on ang na pectoris arteriography ischem c heart d sease Q waves
4 Scand 206 193 1979

gcal Q waves are normally considered indi a myocardial scar following acute myocar rct on due to coronary arteriosclerosis In ons from recent years demonstrated nor near normal coronary arteries in several w th previous acute myocard al infarction thermore several causes of myocard al in other than coronary arteriosclerosis have cribed (1)

ourposes of th s invest gation were to de ne pred ctive value of patholog cal Q waves l agnos s of coronary artery d sease (CAD) describe ECG changes where Q waves are cat ve of CAD

PATIENTS AND METHODS

75 technically sat sfactory select ve coronary aphies were performed n our department n 234 A deta led report has previously been publ shed que nd cat ons and compl cat ons of coronary aphy (5) All nvest gat ons carried out w th Jud hnique (9) were performed for d agnost c reasons ary artery su gery was not ava lable in our hosp t me

Fast ng sup ne 12 lead ECGs were asses ed n a cordance with the M nnesota code (18) Patholog cal Q wa es fulf l the code po nts 1 1 1 2 or 1 3 The ECG were evaluated by two observers independently he e sults were compared and d sagreements sol ed by mu u l consent

The follow ng def n t ons were used n the analyses 1) left ventricular hypertrophy = po nts 3 1 and 3 3 2) left ax s 30° through 90° n leads I II III (po nt 2 1) 3) right bundle branch block RBBB) po nt 7 2 4) ntraventricular block po nt 7 4 5 incomplete left bundle bran h block (LBBB) 7 6 and n ludes pat nts with left hem block (19) None of the pa ents had r ght ventricular hypertrophy

The degree of stenosis of a coronary artery has been assessed in the p oject on where the stenos s s most pr nounced (6) CAD denotes mo e than 75% steno i one of the major coronary arter es e right coronary artery the c rcumflex or the anter or descend ng bran h of th left coronary artery None of the pat ents had left m n CAD

χ^2 test and Fisher s test were used for stat st cal com parison between group

RESULTS

Pathological Q waves were found in 78 patients 66 males aged (mean+S D) 48 1+12 7 years and 12 females aged 48 8+10 7 years (Table I) Of these pat ents 54 (69 2%) had CAD 7 had at least 75% stenos s in three vessels 20 had 75% stenosis n two and 27 had 75 stenosis in one vessel

A s gn f cant improvement in pred ctive value was obtained by excluding patients w th left ven tricular hypertrophy intraventricular incomplete LBBB and RBBB (Table II) Fourteen (43 8%) of 32 pat ents w th these f nd ngs in the ECG had CAD compared to 40 (87%) of 46 patients without these changes ($p<0\ 0005$)

Accord ng to the M nnesota code the most pro nounced Q waves are coded as 1 1 less pronounced Q waves as 1 2 and the least pronounced Q waves

Abb e at ns CAD coronary artery d sease ECG electrocard ogram BBB bundle branch block LBBB = left BBB RBBB right BBB

Table I *Prevalence of pathological Q waves and CAD in 234 consecutive coronary arteriographies*

	No of pats		
	Without CAD	With CAD	Total
Minnesota Q code			
1 1	6	24	30
1 2	13	21	34
1 3	5	9	14
LBBB	8	1	9
No Q code	102	45	147
Total	134	100	234

as 1 3 Among the 46 patients no significant differences in prevalence of CAD were found between patients coded as 1 1 (n=16 1 without CAD) 1 2 (n=23 4 without CAD) or 1 3 (n=7 1 without CAD) In the group of 46 patients 2 had significant mitral valve incompetence probably because of papillary muscle rupture after myocardial infarction 4 had aortic stenosis and/or incompetence and one hypertrophic obstructive cardiomyopathy with mitral incompetence 6 of these 7 patients had CAD Thirty five of the 46 patients had angina pectoris and 34 of these 35 patients had CAD while 6 of 11 patients without angina pectoris had CAD (p<0 01)

The Minnesota code Q QS criteria fulfilled by the 46 patients were as follows (figures in parentheses *indicate number of patients with CAD*) *1)* Q/R amplitude ratio 1/5 or more plus Q duration of at least 0 02 sec in any of leads I II V_{2-6} n=14 (n=13) 2) Q duration of at least 0 03 sec in any of leads I II V_{2-6} n=3 (n=2) 3) QS patterns in each of leads V_1 and V_2 n=9 (n=7) 4) Q duration of at least 0 03 sec in lead III plus any Q wave of at least 0 1 mV in aVF n=14 (n=12) 5) Q duration of at least 0 03 sec and R wave of at least 0 3 mV in aVL n=2 (n=2) 6) R wave decreasing to 0 2 mV or less or QS pattern when R wave is present in adjacent leads to the right of the chest V_{2-6} n=4 (n=4)

DISCUSSION

Description of the relationship between myocardial infarction CAD and pathological Q waves is based on patho-anatomical studies (14 15 16) Myers pointed out already in 1950 that ventricular hypertrophy (12) and BBB (13) were associated with pathological Q waves although myocardial infarction could not be demonstrated at a[illegible] the introduction of selective coronary a[illegible] and left ventricular angiography it wa[illegible] strated that in patients with CAD withou[illegible] lar hypertrophy LBBB or left hemiblock accurately predicted the presence and left ventricular dyssynergy (11) Also [illegible] with previous myocardial infarction Q [illegible] perfect indicators of left ventricular [illegible] (6) We found that pathological Q waves [illegible] erroneous diagnosis of ischemic heart [illegible] patients with hypertrophic obstructi[illegible] myopathy (7) Gau et al (4) also found [illegible] ical Q waves misleading in relation to 6 of 10 patients with congestive and in [illegible] *obstructive cardiomyopathy* At least so[illegible] patients had left anterior hemiblock whic[illegible] shown by Farnham and Shah (3) to [illegible] anteroseptal myocardial infarction H[illegible] (8) found near normal coronary arteries [illegible] patients with pathological Q waves 11 of [illegible] left ventricular hypertrophy No inf[illegible] available about axis deviation intraventr[illegible] duction disturbances or the number of p[illegible] left hemiblock seen on the illustrations [illegible] al (2) investigated 50 patients with ECG [illegible] of inferior transmural myocardial infar[illegible] the same criteria as we did They found [illegible] CAD in the right coronary artery in 43 p[illegible] in the left anterior descending artery in the [illegible] *ing 7 Excluding patients* with left [illegible] hypertrophy BBB and aortic valve disease [illegible] al (10) found CAD in 47 of 50 patients [illegible] logical Q waves CAD was found in 1[illegible] 162 patients with codable Q waves b[illegible]

Table II *Prevalence of CAD in 78 pat[illegible] pathological Q waves in relation to left [illegible] hypertrophy ventricular conduction dis[illegible] and left axis deviation*

	No of p[illegible]
	Without CAD
Left ventricular hypertrophy	7
Intraventricular block	2
RBBB	6
Incomplete LBBB	1
Left axis deviation	2
No conduction disturbances left ventricular hypertrophy or left axis deviation	6

ᵗᶜlch et al found CAD in 35 (76%) of 46 20) and in 103 (94%) of 109 men (21) below of age with pathological Q waves The on of patients with CAD thus varied from 0% It depends on patient selection in with increasing proportion of patients with ectoris and decreases with increasing pro- of patients with hypertension valvular ease and cardiomyopathy In most reports ng Q waves and CAD specific information ing about hypertrophy QRS axis and/or

tudy shows that pathological Q waves are predictors of coronary artery disease ex ents with left ventricular hypertrophy deviation QRS duration of at least 0 12 incomplete LBBB in the ECG The predic ue is further increased by adding informa angina pectoris It should be stressed found no difference in the predictive value fferent types of coded Q waves

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Famılıal Occurrence of Intracranıal Aneurysms

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ACT Intracranıal aneurysms occurrıng ın mılıes are reported As a result of the dıscov plenıc artery aneurysms ın one of the fam nbers the relatıon between intracranıal an , and aneurysms in other sıtes is dıscussed forward that aneurysms mıght be a part of a zed connectıve tıssue dısease, and the relatıon aneurysms and some connectıve tıssue dıs stressed At present extensıve angıographıc *atıons ın famıly* cases cannot be recom ın every famıly

rds cerebral aneurysms splenıc artery aneu fibromuscular hyperplasıa connectıve tıssue

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nılıal *occurrence of ıntracranıal aneurysms ıs* ı 1977 there were only 47 such famılıes ın approxımately 100 cases descrıbed ın the re (7) Many authors have speculated about valence and the genetıc pattern of famılıal atıon of aneurysms but to clarıfy the pıcture sentıal that addıtıonal cases are reported

veen 1970 and 1976 90 cases of subarachnoıd *rrhage* were dıagnosed at our department In hese cases a ruptured ıntracranıal aneurysm ocumented Three famılıes ıncludıng more ne member wıth ıntracranıal aneurysms were among these cases The three famılıes wıll be ed here

CASE REPORTS

I (Fıg 1)

Female born ın 1935 (no 19 ın Fıg 1) She was d to hospıtal because of hypertensıon Her famıly ıncluded several members wıth strokes She had roubled by headache for some years and had un ıe two operatıons for varıcose veıns She had been l wıth *l* thyroxın for an atoxıc goıtre examınatıon the blood pressure wıthout treatment 90/115 She had a slıght thyroıd enlargement and se synchronous bruıt was heard just left of the ıcus

Because of her remarkable famıly hıstory and her own strong wısh to know whether she had the same fındıngs as her brother and daughter (vıde ınfra) a cerebral angıography was carrıed out No aneurysms were demonstrated A selectıve renal angıography also ıevealed nor mal fındıngs Because of the bruıt recorded at the examınatıon an abdomınal angıography was carrıed out Three aneurysms 3–4 mm ın sıze were found ın the branches of the splenıc artery just near the splenıc hılus (Fıg 2)

An operatıon on these aneurysms was not regarded necessary for the moment The blood pressure was satısfactorıly controlled wıth propranolol and bethanıdıne

She came to the hospıtal 15 months later because of abdomınal paıns The bruıt from the splenıc artery aneurysms was no longer demonstrable possıbly because of thrombotısatıon of the aneurysms The paıns dısappeared and no new abdomınal angıography was carrıed out

Case B The brother of case A (no 16 ın Fıg 1) He dıed 36 years old of subarachnoıd haemorrhage due to a ruptured aneurysm on the left mıddle cerebral artery documented at autopsy

Case C The daughter of case A (no 27) She dıed ?? years old of subarachnoıd haemorrhage due to a ruptured aneurysm on the left ınternal carotıd artery The rupture occurred 7 months after a normal delıvery

In addıtıon to these three cases wıth documented aneurysms there were three other famıly members wıth *conceıvable ıntracranıal aneurysms*

The mother of case A (no 11) dıed suddenly 54 years old and her death certıfıcate read Malıgnant hypertensıon + cerebral haemorrhage Autopsy was not performed

The aunt of case A (no 4) dıed 51 years old Her death certıfıcate read Cerebral haemorrhage She was paralysed 6 months before she dıed Autopsy was not performed

The uncle of case A (no 5) dıed suddenly 61 years old He fell down from a ladder and had just before complaıned of headache Autopsy was not performed

Famıly II

Case D Female aged 57 She had suffered from a mıld hypertensıon for some years In 1972 she got a subarachnoıd haemorrhage and an aneurysm on the left mıddle cerebral artery was lıgated wıth satısfactory result

Case E The brother of case D At the age of 60 he suddenly lost conscıousness and bılateral carotıd angıography demonstrated an aneurysm on the anterıor communıcatıng artery Hypotensıve treatment wıth α

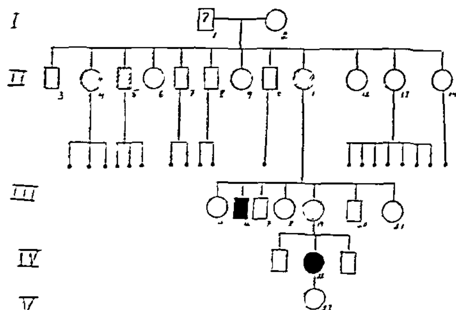


Fig 1 Famil
the relations
■ = Document
aneurysms
intracranial an
splenic artery a
Circles indica
rectangles male

methyldopa and thiazide diuretic was started An angiography three months after the rupture showed that the aneurysm had declined in size

Family III

Case F Male aged 49 with a high consumption of alcohol for several years suddenly experienced weakness in the limbs and his condition worsened on the following day A cerebral angiography demonstrated an aneurysm on the left internal carotid artery just at the beginning of the posterior cerebral artery The aneurysm by ligature and the patient has been well the exception of dizziness

Case G The sister of case F She had be sive since her last pregnancy at the age of of age she got a left facial palsy and headac angiography showed a narrow portion of the cerebral artery which was interpreted as 33 she again experienced sudden headache left facial palsy and aphasia. A new angiog



Fig 2 Abdom
graphy from cas
ing three splenic
aneurysms (arr

.rrow ng of the right middle cerebral artery In ing years she suffered from attacks of headache blindness loss of memory and sometimes weak e left extremities At 36 years of age during a on operation she developed a complete left is and d ed soon thereafter

haematoma in the right hemisphere reaching ventricles was found at autopsy The cerebral howed only a very slight degree of arterio- *On the other hand a small aneurysm was dem* on the right middle cerebral artery Repeated from this aneurysm with consecutive arterial ght poss bly have been mistaken for thrombosis iographies

DISCUSSION

al aneurysms are regarded as congenital cases and by studying the familial ice one *can get an idea of the significance* factors The exact prevalence however letermined only by extensive angiographic of the affected families The real prevalence ibly far more frequent than indicated by in the literature because some family s have asymptomatic aneurysms or intra aneurysms may be overlooked at autopsy of als dying from other causes

rysms in the familial cases tend to rupture at er age than in the non familial cases Fur re the occurrence of aneurysms at identical two relatives is more than twice as frequent cted (7)

xact role and nature of genetic factors in the cases is not known As Bannerman et al out (1) it is probably a very heterogeneous on in which genetic factors fortuitous aggregation and the relation to known ary diseases such as Ehlers Danlos syn may play a part

nal aneurysms may be related to different s especially those involving the connective such as Ehlers Danlos syndrome polycystic s angiomas coarction of the aorta Marfan s me and fibromuscular hyperplasia (FMH) of s The association between *intracranial* sms and aneurysms in other sites is not a equently reported phenomenon Intracranial sms are most commonly associated with re splenic artery aneurysms (2 10 11 12 17 can also occur together with FMH in renal arteries (2 6 13) Other associations are own

The aetiology of cerebral aneurysms is usually congenital defects in the arterial wall Other aneurysms that may have a congenital aetiology include renal splenic hepatic and coeliac artery aneurysms (3 15) Aneurysms on the superior mesenteric artery and its branches however are regarded as mycotic in origin in most cases (5) and aneurysms on the femoral and popliteal arteries almost exclusively have an arteriosclerotic gene sis (5)

With this background it is concluded that con genital aneurysms just like FMH sometimes must be regarded as a generalized condition of conne tive tissue Perhaps one should include some other connective tissue diseases and talk about a special defective connective tissue syndrome Patient A developed splenic artery aneurysms while two of *her relatives suffered from intracranial aneurysms* Probably there exists a hereditary disposition for weaknesses in the arterial wall In what arteries these weaknesses contribute to the development of aneurysms may be dependent on difference in histological structure local haemodynamic or for tuitous factors

An entity with great similarity to arterial aneurysms is FMH This condition though most common in the renal arteries is a generalized condi tion of small and medium sized arteries Besides the renal arteries FMH may also engage the splenic artery the coeliac artery the carotid and vertebral arteries the mesenteric arteries and the iliac arteries (2 4 6 19) As mentioned before FMH may be associated with intracranial aneurysms (6 13 19) Familial occurrence of FMH has been de scribed (16) Wylie et al (19) discuss whether there exists a common aetiology for FMH and intra *cranial aneurysms The most convincing evidence* is their histological similarity

Jain (8) suggests that all members of a family in which more than one member has intracranial aneurysms should be investigated He also con cludes that cerebral angiography should be con sidered in closely related patients with polycys tic kidneys Ehlers Danlos syndrome and other similar conditions He also reports successful surgi cal treatment of incidentally discovered non ruptured aneurysms (9) Taking into account the relative rarity of the condition and the risk of radiological and operative procedures it is doubtful whether cerebral angiography is indeed indicated in all these cases Angiography of all members of a

large family (like family I presented here) leads to problems sometimes of a far reaching psychological nature One possibility is to direct the investigations towards members showing certain risk factors for example hypertension

No strict recommendations for the investigation in these cases can be given today—it is advisable to know more about the prevalence first and also to have a very deep insight into the families concerned especially from a psychological viewpoint It is also important to establish firm collaboration with a neurosurgical department and to be familiar with the neurosurgeon s attitude to prophylactic surgical treatment before entering upon extensive family studies

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Alkaline Phosphatase in Women with Osteoporosis

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U ers t of Li nd Malm S eden

ACT Altoghether 1? partially independent ments of bone mass in 100 women with clini k roentgenological signs of osteoporosis were ed to the alkal ne phosphatase activities of the dividuals There was a slight but significant correlation indicating an increasing alkaline itase activity with decreasing bone mass This ion was not caused by interaction of age was no correlation between alkaline phos- activity and clinical or morphological signs of a The changes could not be explained by s It is suggested that a sl ght increase in the phosphatase activity in women with a more osteoporosis is related to bone resorption

rds alkal ne phosphatase osteomalacia osteo-

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rum alkal ne phosphatase is frequently used cal d agnostic work as a screening test of disease ma nly for the disclosure of os ac a or for studies on the consequences for l metabol sm of renal disease and hemo- s

purpose of this study was to relate this vari alkal ne phosphatase to parameters of bone and composit on in a series of women with l s gns of osteoporosis

SELECTION OF PATIENTS

study were selected 100 women who had sought d adv ce because of back ache and who had g cal ev dence of sp nal osteoporos s Cl n cally was a large variat on w th cases rang ng from doubt atholog cal to severe osteoporosis w th deform ty of nal column and mult ple fractures The women ll post menopausal their age at the t me of the in ation was 63 3±7 6 years Their menopausal age en 46 7+4 5 (mean+S D)

METHODS

Alk l ne pl ospl at se

The alkal ne phosphatase was est mated by a mod t ed Busch and Busch method us ng ? am no- me hyl l propanol buffer para n tro-phenyl phosphate as substrate and magnes um as acti ator w th an opt mal pH of 10 8 With th s method the normal variat on n adul s —8 un s with n 95% conf dence l m ts

Sp nal osteopo os s

Rad olog cal dens ty was class f ed 0–4 w th nc ea ng severity of rad ological osteoporo is v ble on lateral rad ograms of the lumbar sp ne (11)

The number of crush fractures 0–5 or more was de term ned from lateral rad ograms of the thora and lum bar sp ne

The vertebral rat o was calculated as the rat o be ween the central he ght and the sag ttal d ameter of the body t the lumbar vertebra located most closely to the central beam in lateral rad ograms of the lumbar sp ne Only n 73 cases the rad ograms were of suff c ent quality for th s measurement

The sp nal ratio is def ned as the rat o between the he ght of the head plus trunk measured n sitt ng pos t on and the total he ght Th s variable is a parameter of sp nal shortening (8)

Il ac crest b ops

A 0 5×1 5 cent meter cyl ndric bone sample was obta ned from the left l ac crest by the method of Burkhardt (2) The un decalc f ed sample was imbedded in methylmetac rylate sect oned and sta ned by a mod f ed Goldner technique The surface and the volume of bone and os teo d n the sect ons were est mated using a po nt and wave pattern engraved on the eye piece of the m croscope (6) Also the osteo d was calculated and expressed as % of total bone S xty four b ops es of suff cient qual ty to be ncluded were obta ned

Gamma absorpt ometry

The bone mass in the forearm was measured by a photon absorpt on techn que (7) The method is sim lar to that of Cameron and Sorensson (3) the ma n d fference be ng the source of rad at on americium ?41 instead of od ne 125 The bone mass was measured 1 and 6 cent meters proxi mally of the dorsal d stal edge of the ulna

Table I *The relationship between alkaline phosphatase and parameters of bone mass*

Variable	No	r	p
Spine			
Radiological density	99	0 21	0 05<p<0 02
Crush fractures	98	0 15	p>0 1
Vertebral ratio	73	−0 10	p>0 1
Spinal ratio	87	−0 12	p>0 1
Iliac crest			
Bone surface	64	−0 26	0 05>p>0 02
Bone volume	64	−0 17	p<0 1
Forearm			
Left 1 cm	93	−0 33	0 01<p<0 001
Right 1 cm	96	−0 24	0 02<p<0 01
Left 6 cm	94	−0 25	0 02<p<0 01
Right 6 cm	90	−0 33	0 01<p<0 001
Metacarpus			
Left	97	−0 22	0 05<p<0 02
Right	97	−0 17	0 1 <p<0 05
Femur			
Left	99	−0 22	0 05<p<0 02
Right	99	−0 27	0 01<p<0 001
Trabecular pattern	95	−0 18	0 1 <p<0 05

Metacarpal and femoral cortices

The cortical thickness was measured on the midshaft of the second metacarpal and the femur in anteroposterior radiograms In both instances the combined cortical thickness was measured and corrected for the width of the bone (1 4)

Femur trabecular pattern

The trabecular pattern of the proximal end of the femur was estimated on anteroposterior radiograms of the hip according to the method of Singh et al (12) Both hips were used for the estimate

tatistics

e relationship between alkaline phosphatase and the various parameters of bone mass was studied by the method of linear correlation It should be taken into account that some of the variables radiological density number of crush fractures and trabecular pattern are non parametric

RESULTS

The alkaline phosphatase for the entire group was 6 7±2 0 units There was no correlation between age and alkaline phosphatase (r=0 04 p>0 1) In 9 out of 15 parameters of bone mass there were significant correlations indicating increasing alkaline phosphatase activity with decreasing bone mass (Table I) In some of the variables there were suggestive relationships with the same tendency in all of the correlations significant or not the tendency was homogeneous (Note that radiological density and number of crush fractures will in rank with decreasing bone mass)

There was no correlation whatsoever the amount of osteoid total or relative mass and alkaline phosphatase (Table II)

Twelve women had alkaline phosph- tivities of 10 or more (10–14 units) They were searched for possible distinguishing no case did the bone biopsy show osteo- one instance the alkaline phosphatase was measured within a few weeks after a vertebr- pression fracture The activity became nor- on In another case the elevated value was shortly after the bone biopsy was taken remaining cases there was no clinical sig- suggesting a close relationship in time wi- In most instances more than one value over limits was recorded The 12 women did not in age from the average of the sample nor there any clinical features distinguishing th

Table II *The relationship between alka- phatase and osteoid*

Variable	No	r	p
Osteoid surface	64	0 00	[illegible]
Osteoid volume	64	0 00	[illegible]
% osteoid surface	64	0 03	[illegible]
% osteoid volume	64	−0 03	[illegible]

DISCUSSION

ıline phosphatase actıvıty of the women ın ly was ıncreased only slıghtly above the ıverage Only a mınorıty of the patıents had y abnormal values

bject of the test was to ıdentıfy patıents tabolıc bone dısease other than ıdıopathıc osıs partıcularly osteomalacıa Clınıcally , not successful and the alkalıne phos actıvıty was not related to the amount of tıssue found ın bone bıopsıes

ts (10) and Keatıng et al (5) demonstrated alkalıne phosphatase actıvıty ıncreased ın healthy women In the present study g only women wıth clınıcal osteoporosıs ı a more narrow age range no such correla ld be demonstrated Therefore the ınverse shıp between bone mass and alkalıne phos actıvıty ıs probably not a result of ınterac ıge

on and Westlın (9) demonstrated that ın wıth femoral neck fracture the alkalıne ıtase actıvıty was elevated durıng the fırst nths after the ınjury No such relatıonshıp ıcture could be demonstrated ın the present

ı the correlatıon coeffıcıents ıt can be seen re ıs a consıderable resıdual varıance ın the · phosphatase data less than 10% of the e ıs explaıned by correlatıon to bone mass relatıonshıp between alkalıne phosphatase luctıon of bone mass found ın thıs study has n prevıously descrıbed The reason for thıs ıshıp ıs not known but ıt ıs suggested that ıdıopathıc osteoporosıs an ıncreased alkalıne atase ıs a sıgn of ıncreased bone resorptıon

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Bone Biopsy in Women with Spinal Osteoporosis

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CT *Il ac crest biopsies were obtained from* ıen 62 of whom had been clinically and cally classif ed as osteoporotics The amount d surface was measured by a histological r cal method It was demonstrated that the of osteoid does not differ between osteopo- nen and control women and that osteomala e in both groups

s bone b opsy osteomalacia osteoporos s
l Scand 206 205 1979

ant feature in idiopathic osteoporosis is nce of pathological laboratory f ndings eless it may be assumed that a group of with s gns of osteoporosis such as back l rad olog cal changes contains one or more n wh ch further d agnostic work in profit nong others Andersson et al (2) and Chal al (4) formulate a hypothesis accord ng to steomalacia is a fairly frequent cond t on in rly poss bly because of malnutrition and rly n women Osteomalacia is in marg nal d ff cult diagnosis The most reliable tool is y the bone b opsy (5)

urpose of the present study was to test the ss of iliac crest biopsy for the d agnosis of lac a in a group of women class fied as os tics

PATIENTS

o cs

) consecut ve women were selected depend ng on ymptoms and rad olog cal s gns of sp nal osteo- All pat ents had been f rst referred because of e On the n t al rad ogram the d agnos s of os s was based on an obv ously low rad olog cal crush fractures or both None of the pat ents had of se ere dietary def c ency malabsorpt on or sease The r alkal ne phosphatase levels were ormal l m ts

Controls

Il ac crest samples were obta ned f om 48 autops e n women in the Department of Forens c Med c ne In luded were ind viduals who had suffered sudden dea h mo tly card acs or death by violence Excluded were nd v duals who were known to be alcohol cs or who had undergone gastro ntest nal surgery The age d stribut on of bo h samples is demonstrated in F g 1

METHODS

Est at n of osteo d

The method and instrument of Burkhardt (3) were u ed In local anaesthesia a small inc s on was made over the il a crest and a cyl ndric 0 5–1 5 cm bone sample was ob- ta ned with a motor-dri en m ller Th s s the method to collect a sample w thout deform ng the cancellous bone

The undecalc f ed samples were mbedded n methyl metacrylate and 4–6 μm sect ons were made n a hard se tion m crotome The sect ons were sta ned by a mod f ed Goldner (6) method In the result ng sl des the osteo d t ssue can be d st ngu shed from the calc f ed material by colour The surface occup ed by bone and osteo d was measured by count ng intersect ons between bone os teo d and a wave pattern engraved on the eye p ece of the m croscope (7) Only trabecular bone was evaluated The abundance of osteo d t ssue was calculated as the per centage osteo d surface of total bone surface

RESULTS

The per cent osteoid was 3 2+4 0 and ? 7+4 0 (average + S D) in osteoporotics and controls re spectively There was no sign ficant d fference be tween the groups As ind cated by the standard deviat ons the variable is skewedly d stributed (F g 2) There was no correlat on between age and per cent osteo d in th s study

DISCUSSION

The skewedness of the data would imply that in osteoporotic women the bone contains no or al most no detectable osteoid whereas n some ind

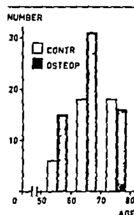


Fig 1 Age distribution of osteoporotics and controls

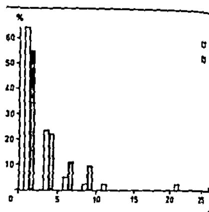


Fig 2 Distribution of osteoid in osteopo
trols

viduals the amount of osteoid is slightly increased because of some skeletal disorder However the same distribution was found in the controls Values below 10% cannot be referred to as pathological This should be compared with the findings of Aaron (1) who proposed that the normal upper limit for osteoid in an English population is 24% of the trabecular surface Only in one of the 62 osteoporotics a definite increase above normal could be demonstrated She was a woman whose symptoms did not differ from the others nor did she have any abnormalities in serum calcium serum phoshorus or alkaline phosphatase in repeated measurements

Our conclusion is that bone biopsy as a routine screening method to detect osteomalacia in women with osteoporosis does not return the efforts invested It should be limited only to patients with signs and symptoms deviating from the usual tern of osteoporosis

Most of the data indicating that osteomalacia is common in old women has been collected in Britain Possibly nutritional habits and other ethnical particularities contribute to the discrepancies Our observations and conclusions are therefore valid only under the present conditions in Southern Sweden

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Erythrocyte Sedimentation Rate n a Population Sample of Women with Special Reference to its Clinical and Prognostic Significance

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CT A comprehensive population study of ged 38–60 was carried out in Goteborg, n 1968–69 The same women were re-studied later, in 1974–75 Erythrocyte sedimenta (ESR) was studied on both occasions A lly significant rise in ESR with age was noted oss-sectionally and longitudinally, which at the increase was related to age and was ort effect The mean annual increase in ESR ut 0 6 mm/h, but there was a significant e between the ages studied, the increment ger in the upper age groups Women with l (here defined as ESR ≥30 mm/h) had lower Hct values than other women Leucocyte ere higher in women with ESR ≥30 mm/h he others, but differences were statistically it only in the upper age groups Serum iron ere lower in women with high ESR, while lues were similar to those in the other wom ificant differences were found for transfer ration (lower in women with high ESR) rol levels were similar, while triglyceride her tended to be or were significantly higher n with high ESR About half of the women R ≥30 mm/h had a possible explanation for reased ESR In no case did an increased ESR to a new diagnosis of clinical significance, 1968–69 or in 1974–75 Nor had any s been missed in women with a high ESR in , according to the re examination six years l except one woman, in whom the diagnosis astic disease was made in the interval be e two examinations had ESR ≤30 mm/h in and women in whom a neoplastic disease nd later had on average no higher ESR in than the others It is concluded that for g purposes, ESR is of very limited value

erythrocyte sedimentation rate age changes ic disease population study women
d Scand 206 207 1979

Erythrocytes separate from plasma at a variable rate which may be elevated or depressed in con nection with disease The erythrocyte sedimenta tion rate (ESR) has been put to wide clinical use since the works of Fåhraeus (7) and Westergren (20) but its clinical significance has been poorly evalu ated ESR may be elevated in apparently healthy in dividuals The reason for the association between various physiological and pathological conditions and raised ESR is not understood in detail but has been attributed to changed properties of the plasma

The main purpose of the present study on ESR was to increase our knowledge of its clinical signifi cance and the aims of this paper are to study 1) the distribution of ESR values in a female population with special reference to differences with age 2) other concomitant laboratory changes in the blood of women with raised ESR 3) the causes of raised ESR in a defined population 4) the prognosis of subjects with raised ESR

STUDY POPULATION

A population study of women in Goteborg Sweden was performed in 1968–69 (1) Altogether 1462 women in the age strata 38 46 50 54 and 60 years were examined They were representative of the total population of women in Göteborg in the ages studied The sample was obtained from the Revenue Office Register The same women were re-examined six years later in 1974–75 when they were aged 44 52 56 60 and 66 The two studies were per formed in a similar way (2) Numbers of participants and participation rates in the two studies are shown in Table I

METHODS

Both studies were carried out during a one year period A date for an examination was settled For menstruating

Table III *ESR in relation to age and intraindividual differences in women who participated in [illegible] with statistical significance of intraindividual differences*

n	1968–69 Age (y)	ESR (mm/h) Mean	S D	1974–75 Age (y)	ESR (mm/h) Mean	S D	Difference Mean	S D	p
333	38	10 8	11 3	44	12 7	12 5	1 9	11 5	<0 01
385	46	11 0	8 4	52	14 9	11 6	3 9	10 2	<0 001
349	50	11 8	7 7	56	16 6	13 2	4 9	11 8	<0 001
163	54	14 2	10 3	60	18 2	13 2	4 0	11 9	<0 001
65	60	18 5	14 3	66	24 1	20 2	5 6	13 4	<0 01
1295		12 0	9 8		15 7	13 2	3 8	11 4	<0 001

Women with high ESR

Other laboratory characteristics Women with high ESR (≥30 mm/h) in 1968–69 were compared with the other women in each age stratum with regard to various laboratory examinations Their Hb concentration Hct leucocyte count serum iron TIBC transferrin saturation serum cholesterol and serum triglyceride values are shown in Table IV The Hb and Hct concentrations were lower in the women with high ESR The differences are statistically significant in all the age strata studied The leucocyte counts were higher in the women with elevated ESR but the differences are statistically significant only in those aged 54 and 60 *Serum iron* levels were lower in women with high ESR (statistically significant differences in all age strata) while TIBC was similar the only statistically significant difference being for women aged 54 Significant differences were found in all age strata for transferrin saturation No significant differences were found for cholesterol levels Triglyceride levels were somewhat higher in women with high ESR but the difference is statistically significant only for women aged 54 and the total sample

Possible explanation In the study performed in 1968–69 altogether 78 women had an ESR ≥30 mm/h Possible causes of the elevated rate were found in 36 rheumatoid arthritis 9 arthritic symptoms 8 systemic lupus erythematosus 2 other collagenosis 1 chronic alcoholism 1 severe anaemia (Hb <100 g/l) 2 uraemia 2 pregnancy 1 cancer 1 ulcus cruris 1 urinary tract infection 2 chronic bronchitis 4 chronic osteomyelitis 1 Salmonella infection 1 The ESRs of the 42 women with no explanation for their raised values were 30–34 mm/h in 20 35–39 mm/h in 16 and ≥40 mm/h in 7 All these women were symptom free and [illegible] time of the study

Of the 141 women with ESR ≥30 [illegible] 75 76 had a possible explanation for the [illegible] rate rheumatoid arthritis 16 arthritic [illegible] 28 systemic lupus erythematosus 1 [illegible] poralis 1 other collagenosis 1 liver [illegible] hyperlipidaemia 3 urinary tract infection [illegible] pyelonephritis 7 uraemia 2 cancer [illegible] psoriasis 1 ulcus cruris 2 gangrene 1 bronchitis 5 other infection of the [illegible] 3 thyroiditis 1 No apparent cause of the ESR was found in 65 women All were [illegible] free and felt well Their mean ESR was [illegible] (S D 10 1) compared to 45 8 mm/h (S D [illegible] the 76 women with a possible cause of [illegible]

Prognosis Of the 1462 women [illegible] 1968–69 27 died during the six year [illegible] tween the two studies 4 (5 2%) of those [illegible] ≥30 mm/h and 23 (1 8%) of those with [illegible] mm/h *The difference is not statistically* [illegible] The causes of death in three of the [illegible] ESR ≥30 mm/h were valvular heart [illegible] heart insufficiency cancer of the [illegible] metastases and diabetes with renal [illegible] All these diagnoses were known bef[illegible] (Table V) The fourth woman drowned

Six of the women who had a possible [illegible] for an increased ESR in 1968–69 did not [illegible] in 1974–75 in addition to the three [illegible] *No new diagnosis during the period* [illegible] two studies was recorded in the 27 [illegible] ESR ≥30 mm/h in 1968–69 who [illegible] 1974–75 Twenty of these women had [illegible] mm/h and seven <30 mm/h when [illegible] 1974–75

Comparison between women with ESR ≥30 and <30 mm/h in 1968–69

SR <30 mm/h			ESR ≥30 mm/h			
	Mean	S D	*n*	Mean	S D	*p*
bin concentration (g/l)						
56	135	10	15	129	10	<0 05
13	136	11	18	130	11	<0 05
33	138	10	15	124	23	<0 001
52	139	9	18	132	12	<0 05
59	139	8	12	130	6	<0 001
13	137	10	78	129	14	<0 001
rit (%)						
55	39 1	2 4	15	37 7	2 5	<0 05
09	39 6	2 8	18	38 0	1 9	<0 05
83	39 6	2 7	15	36 1	5 5	<0 001
62	40 1	2 6	18	38 5	2 7	<0 05
58	40 6	2 4	12	38 9	2 1	<0 05
76	39 7	2 7	78	37 8	3 4	<0 001
s (10^9/l)						
47	5 54	1 76	15	5 85	2 44	NS
01	5 49	1 68	18	6 03	1 73	NS
80	5 30	1 59	15	5 89	1 87	NS
67	4 94	1 46	18	6 68	2 11	<0 001
68	5 02	1 41	12	6 05	2 50	<0 05
59	5 36	1 65	78	6 12	2 15	<0 001
n (μmol/l)						
55	19 0	8 1	15	13 3	3 4	<0 05
12	18 1	8 1	18	12 5	7 2	<0 05
83	18 6	7 0	15	12 9	6 1	<0 05
60	20 2	6 8	18	15 0	5 3	<0 001
69	20 2	5 3	12	13 8	3 8	<0 001
79	18 8	7 5	78	13 4	5 6	<0 001

Age (y)	ESR <30 mm/h			ESR ≥30 mm/h			
	n	Mean	S D	*n*	Mean	S D	*p*
TIBC (μmol/l)							
38	355	62 1	10 8	15	62 8	11 2	NS
46	412	62 3	9 7	18	63 0	9 9	NS
50	383	61 7	9 0	15	60 1	9 9	NS
54	160	60 8	8 6	18	55 4	6 5	<0 05
60	69	60 5	9 5	12	58 9	9 4	NS
Total	1 379	61 7	9 7	78	60 1	9 9	NS
Transferrin saturation index (%)							
38	355	31 5	14 2	15	22 1	7 3	<0 05
46	412	30 4	14 3	18	21 2	13 0	<0 05
50	383	31 2	12 5	15	22 4	10 2	<0 05
54	160	34 0	11 9	18	27 6	11 1	<0 05
60	69	34 2	9 5	12	24 2	8 5	<0 05
Total	1 379	31 5	13 3	78	23 5	10 2	<0 001
Cholesterol (mmol/l)							
38	355	6 3	0 9	15	6 2	1 1	NS
46	412	6 8	1 4	17	7 0	1 5	NS
50	383	7 2	1 1	15	7 2	1 3	NS
54	160	7 3	1 1	18	7 7	1 3	NS
60	68	7 4	0 9	12	7 3	1 0	NS
Total	1 379	6 8	1 2	77	7 1	1 3	NS
Triglycerides (mmol/l)							
38	355	1 1	0 4	15	1 3	0 7	NS
46	412	1 2	0 7	18	1 4	0 6	NS
50	383	1 3	0 6	15	1 5	0 4	NS
54	160	1 4	0 7	18	1 7	0 8	<0 05
60	69	1 4	0 6	12	1 1	0 3	NS
Total	1 379	1 2	0 6	78	1 4	0 6	<0 05

of the 42 women with no explanation for an d ESR in 1968–69 did not participate in in addition to one woman who had died he non participants had moved abroad and contacted the other two related at a tele iterview that they had arthritic symptoms : not on treatment

n of the participants still had ESR ≥30 hen studied in 1974–75 no definite new s was recorded An elevation of serum ring the six year interval between the two could possibly explain the raised ESR in one Among the 23 women without an explana their raised ESR in 1968–69 and an ESR h in 1974–75 (Table V) new diagnoses in six liver cirrhosis chronic ic leucaemia arthritis myocardial infarc one case each and hyperlipidaemia in two

Incidence of malignant tumours Except for one woman in whom the diagnosis of leucaemia was made later none of those who had ESR ≥30 mm/h in 1968–69 was in 1974–75 known or found to have neoplastic disease which had not been known in 1968–69 It is noteworthy that the woman with leucaemia had a normal leucocyte count in 1968–69 and an ESR <30 mm/h in 1974–75 although she had not been treated

Table VI shows the ESR in 1968–69 of women in whom breast cancer or gynaecological cancer was detected between the two studies and who attended the study in 1974–75 None of them had ESR ≥30 mm/h in 1968–69 Mean ESR in 1968–69 of ten women with breast cancer was 9 8 mm/h (S D 6 4) and of nine with gynaecological cancer 10 8 mm/h (S D 7 9) i e levels similar to or lower than those in the total population sample

Table V *Number of participants and non participants in 1974–75 among women with ESR ≥30 mm/h in 1969–69 who had or had not an explanation for the raised ESR at that time*

	Possible explanation in 1968–69	No probable explanation in 1968–69
Non participants in 1974–75	9	4
Dead	3	1
Other	6	3
Participants in 1974–75	27	38
ESR ≥30 mm/h in 1974–75	20	15
ESR <30 mm/h in 1974–75	7	23

Table VII shows ESR in 1968–69 and the diagnoses of 11 women who at that time were not known to have cancer but who died from cancer between the two studies Their average ESR (mean 9 0 mm/h, S D 4 3) was not higher than that of other women in the population sample

DISCUSSION

ESR in previous population studies

There are few previous data on ESR in subjects who are representative of the general population in the area studied In one previous Swedish study from Kristianstad (13) the ESR of women was reported to be similar to that found in our study but another Swedish population study from Eskilstuna (16) using the Wintrobe method reported somewhat higher values In both the above studies ESR was found to increase with age and to be higher in women than in men We also found a somewhat higher mean ESR in 50-year-old women (12 mm/h) compared with that 8 mm/h reported from Goteborg in men of the same age who had been studied by the same techniques (19)

Definitions of normal and high ESR

Westergren (21) was the first to discuss an upper normal limit for ESR—7 mm/h in women—but later he proposed that 10–12 mm/h and even higher for patients above 50 years of age might be a more practical limit in clinical use Borchgrewink et al (3) studied ESR in a Norwegian series of blood donors 1390 of whom were women In agreement with previous studies they found that ESR [illegible] with age and they proposed 20 mm/h as [illegible] screening limit for female blood don[illegible] Swedish study (6) of 1011 female [illegible]

Table VI *ESR in 1968–69 of women [illegible] study in 1968–69 or in the interval up to [illegible] examination in 1974–75 were found to [illegible] cancer or gynaecological cancer (sam[illegible] time of the study in 1974–75)*

M d = missing data

Subj no	Year of diagnosis	Age at the time of diagnosis (y)	ESR (mm/h) 1968–69
Breast cancer			
1	1968	60	5
2	1969	47	8
3	1970	52	5
4	1970	56	18
5	1971	49	3
6	1973	51	22
7	1973	65	13
8	1974	60	17
9	1974	60	9
10	1974	60	3
Gynaecological cancer			
1	1968	46	7
2	1970	40	28
3	1970	48	17
4	1971	53	2
5	1972	42	2
6	1973	43	14
7	1973	51	17
8	1974	52	4
9	1974	52	11

Table VII *ESR in 1968–69 of wom[illegible] diagnosis of cancer at that time but who [illegible] cancer before the second examination in [illegible]*

Subj no	Year of death	Age at death (y)	Diagnosis
1	1970	48	Bronchial cancer
2	1970	56	Glioblastoma
3	1971	53	Uterus cancer
4	1972	53	Ovarial cancer
5	1972	57	Vesical cancer
6	1973	42	Breast cancer
7	1973	43	Breast cancer
8	1973	50	Ovarial cancer
9	1974	55	Uterus cancer
10	1974	56	Ovarial cancer
11	1974	66	Intestinal cancer

employees ESR was also found to in with age and the values were somewhat an in the present study The authors sug at the upper normal limit in women should n/h below the age of 50 and 30 mm/h above

xpert Panel on the ESR set up by the ional Committee for Standardization in blogy (10) has not fixed limits for normal t stated that a range which includes 90 or the local healthy population should be con normal and that this limit should be ied nationally or regionally Their proposal vell with our arbitrary definition of high 30 mm/h which was found in 78 (5 3%) of omen in 1968–69 and in 141 (10 9%) of 1295 in 1974–75 The arbitrarily chosen cutting greed well with the borderline levels for the centiles of ESR in women below the age of for the upper 10 centiles in women above of 50

relation to age

evious workers (3 6 13 16) we found in ctional as well as longitudinal studies that icreases with age This means that the s with age are mainly real and not cohort Our results also showed that the changes in alues were mainly caused by small changes t participants and not by large changes in a the intraindividual differences were evenly ited on both sides of the mean differences vast majority of values were near the mean

relation to other laboratory data

sociation between raised ESR and decreased d Hct is well documented (6 15 22) and ted by our results We also found statistically cant differences in serum iron levels and rin saturation between women with and it raised ESR (low values with raised ESR) leucocyte counts were higher in women with without increased ESR but differences were ically significant only in the upper age groups the total population This means that if high cyte counts are considered to reflect acute ions such infections are not main reasons for sed ESR

found no or only a slight association between ESR and high cholesterol and triglyceride Bottiger (4) found a significant relationship between ESR and serum lipids and Bottiger et al (5) that ESR was significantly raised in apparently healthy persons who at the time of a health exami nation were markedly hyperlipidaemic An associa tion between increased lipid levels and raised ESR has also been reported by some investigators (15 18) but not by some others (14) This discrepancy between studies might be explained by different ways of analyzing the data We did not find any significant differences in lipid levels between wom en with and without increased ESR except for triglycerides in the case of women aged 54 and in the total sample We plan to study this question in more detail in a subsequent paper

Clinical significance of increased ESR

During the last 50 years it has been generally ac cepted that a healthy person should have a nor mal ESR and the ESR examination has been used all over the world to separate disease from health The possibility has been discussed that a raised ESR might be caused by a hidden disease (4) or by a bad state of nutrition (15) In the study by Pincherle and Shanks (15) all but three of 41 subjects with an ESR >20 mm/h had an apparent cause of the raised level Borchgrewink et al (3) found among blood donors 47 women with ESR >20 mm/h 20 of whom had no probable explanation for the increase This finding is in agreement with the present study where more than half of the women with ESR ≥30 mm/h had no apparent cause in either 1968–69 or 1974–75

Increased ESR did not lead to a new diagnosis in any of the 1461 women studied in 1968–69 even though they were examined in many other respects too The follow up study six years later showed that no diagnosis had been missed which could have explained the raised FSR in 1968–69 New di agnoses were recorded at the follow up in seven women with ESR ≥30 mm/h in 1968–69 who at that time had no probable explanation for an increased ESR but it is to be noted that six of them had an ESR <30 mm/h at the follow up Furthermore women in whom cancer was detected later had no higher ESR in 1968–69 than the other participants in the population study

The outcome for the women in the present study agrees with that for a male population in Goteborg (19) for which a long term follow up did not reveal any difference in ESR between those who died later and those who remained healthy In contrast to the

view of Pincherle and Shanks (15) we conclude that the ESR is of limited value as a screening method in health surveys and may be omitted in such studies

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Small Cell Carcinoma of the Lung
Relation of Calcitonin to Bone Marrow Metastases, Parathormone and Gastrin

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CT The relations of calcitonin concentra he presence of bone marrow metastases and ncentrations of calcium, parathormone and n serum were investigated in 74 untreated with small cell carcinoma of the lung Cal oncentrations were enhanced in two thirds of nts while serum calcium concentrations mal in all In 19 of 57 patients parathormone ations were slightly above the normal range oncentrations of parathormone and calcito- not correlated Bone marrow metastases nfluence on the concentration of serum cal Finally, a small inverse correlation between entrations of gastrin and calcitonin in serum ned The results resemble those of the cal roducing medullary carcinoma of the supporting the suggestion of an ectopic f hypercalcitoninemia in small cell carcinoma ng

ds bone metastases calcitonin gastrin PTH ll carcinoma

d Scand 206 215 1979

alcitoninemia has been found in malignant s in particular in patients with medullary ma of the thyroid (1 13) and lung (8 10) and cancers (5 9) The hypercalcitoninemia in ncer appears to be related to the histologic e Thus Silva et al (10) found particularly ncentrations of serum calcitonin in patients nall cell carcinoma and adenocarcinoma of g and in a previous study two thirds of s with small cell carcinoma had hypercal emia at the time of diagnosis (8) The rela p between hypercalcitoninemia and cell type cancer may be indirect as the frequency of bone metastases is higher in patients with small cell carcinoma and adenocarcinoma than in patients with carcinomas of other cell types (7)

Accordingly we found it worthwhile to study the relation of serum calcitonin to the occurrence of bone marrow metastases in patients with small cell carcinoma In addition the concentrations of calcium parathormone and gastrin in serum were measured since these substances influence calcitonin secretion

PATIENTS AND METHODS

Blood samples were taken after an overnight fast from 74 patients with untreated small cell carcinoma of the lung The concentrations of calcitonin (1) parathormone (4) gastrin (12) and calcium in serum were determined Parathormone was analysed in 57 and gastrin in 69 of the patients

The patients underwent a clinical staging program to disclose the extension of the disease outside one lung and mediastinal and supraclavicular lymph nodes (advanced disease) In addition to clinical and biochemical routine investigations at least chest X ray one bone marrow biopsy with aspiration from the posterior iliac crest and peritoneoscopy with liver biopsy were performed According to the results of these staging procedures patients were divided into 3 groups (R) patients with regional disease i e confined to one lung mediastinal and supra clavicular lymph nodes (A) patients with advanced disease but without verified bone marrow metastases and (B) patients with histologically verified bone marrow metastases

RESULTS

All serum calcium concentrations were below the upper limit of the reference value (2 20–2 70 mmol/l) In 4 patients serum calcium was just below the lower limit the lowest value being 2 13 mmol/l but concomitant hypoalbuminemia was found in all

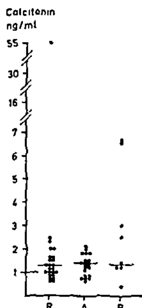


Fig 1 Concentrations of serum calcitonin related to stage of disease in patients with untreated small cell carcinoma of the lung *R*=regional disease (confined to one lung and mediastinal and supraclavicular lymph nodes) *A*=advanced disease without verified bone marrow metastases *B*=advanced disease with histologically verified bone marrow metastases The normal upper limit of serum calcitonin is 1 ng/ml (mean +2 S D)

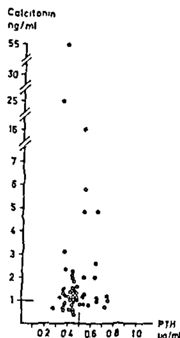


Fig 2 Basal concentrations of calcitonin and [illegible] mone in serum from 57 patients ● = patients [illegible] bone marrow metastases The normal upper li[illegible] parathormone is 0 5 µg/ml

these 4 patients The median serum calcium value for all patients was 2 40 mmol/l

Fig 1 shows calcitonin concentration in relation to stage of disease and bone marrow involvement Considering the distribution of calcitonin concentrations and median values no significant differences were observed between the three groups

In Fig 2 the concentrations of parathormone are ated to calcitonin concentrations One third of e patients had slightly elevated levels of parathormone but no correlation between parathormone and calcitonin concentrations was found either in patients with or without verified bone marrow involvement

Fig 3 shows the relation between gastrin and calcitonin concentrations in serum Increased gastrin concentrations are related to the low levels of calcitonin while gastrin is within the normal range in most patients with significantly elevated serum calcitonin ($p \approx 0$ 10 Spearman test)

DISCUSSION

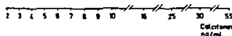
A relation between gastrin and calcitonin in serum has been noticed previously in patients with neoplastic diseases e g calcitonin concen[illegible] serum were significantly elevated in pa[illegible] gastrin producing tumors while gastrin con[illegible] tions were significantly decreased in p[illegible] calcitonin producing medullary carcino[illegible] thyroid (11) In the present investigation [illegible] tion between gastrin and calcitonin con[illegible] appeared similar to that observed in med[illegible] cinoma of the thyroid

Hypercalcemia is extremely rare in p[illegible] small cell carcinoma of the lung (3) and [illegible] in this study had normal concentrations of [illegible] The concentration of calcitonin was [illegible] creased in two thirds of the patients and [illegible] displayed concentrations otherwise [illegible] medullary carcinoma of the thyroid (1[illegible] ficult to explain this observation by [illegible] parathormone because the basal conce[illegible] calcitonin and parathormone did not [illegible] Deftos and Parthemore (6) did not find [illegible] tion between basal concentrations of para[illegible] and calcitonin in patients with medullary ca[illegible] of the thyroid In their study [illegible] parathormone concentrations were eleva[illegible] patients with hyperplasia of the para[illegible] hypercalcemia while their remaining pa[illegible]

thyroid origin which is in contrast to the findings in patients with small cell carcinoma where hypercal citoninemia appears to be related to an ectopic source of calcitonin (10) This was further evidenced by the demonstration of calcitonin in tumor tissue from two patients with small cell carcinoma (2) and is supported by the results presented here

ACKNOWLEDGEMENTS

The work was supported by King Christian Xs Foundation and the Danish MRC



r asal concentrations of gastrin and calcitonin in m 69 patients The normal upper limit of gastrin ml (mean +2 S D)

lcitoninemia had normal calcium and mone concentrations Thus the present resemble those from patients with calcitoducing medullary carcinoma of the thyroid ugh two thirds of our patients had hypercal mia only 19% had histologically verified arrow metastases Bone marrow biopsy with on as performed in this study is the most e to demonstrate bone marrow involvement l cell carcinoma of the lung (7) and some with histologically verified bone marrow ises did have normal calcitonin concentra ig 1) Consequently calcitonin concentra ere related neither to the presence of bone metastases nor to the extension of the dis

et al (10) have also demonstrated hypercal emia in patients with lung cancer Except for ses of epidermoid carcinoma with marginally ed concentrations all their cases with ele serum calcitonin were confined to patients denocarcinoma and small cell carcinoma 'er it appears from their data that patients lenocarcinoma and hypercalcitoninemia usu id verified bone metastases This difference en small cell carcinoma and adenocarcino ppears to be fundamental So hypercal emia in adenocarcinoma seems to be of

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Multiple Attacks of Jaundice Associated with Repeated Sulfonamide Treatment

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rom the Department of Infectious Diseases Östra Sjukhuset and the First Department of Pathology Sahlgrenska Sjukhuset University of Goteborg Goteborg Sweden

ACT Four women who were treated with nides because of recurrent urinary tract in experienced adverse liver reactions with during their third, fourth and fifth course of nt respectively In spite of this, sulfonamide nt was reinitiated some years later Adverse actions with jaundice recurred on all occa he clinical picture of the liver reactions was guishable from that of viral hepatitis and a s-like reaction was also seen histologically f fibrosis appeared histologically after a third of jaundice associated with sulfonamides in ient but otherwise no persisting abnormali e noted

ds sulfonamide jaundice drug jaundice

d Scand 206 219 1979

- injury is a rare but considerable adverse n to sulfonamide treatment A review of this n published in 1967 (2) revealed 106 cases of imide induced liver reactions 96 of which ported before 1947 This cannot be the true ice since only 51 cases of sulfonamide in hepatic injury were notified in Sweden during 5 (4)

irrent jaundice after repeated exposure to amides has been reported in association with stic provocative exposure The present re escribes four women in whom sulfonamide ent was reinitiated in spite of previous ex ce of adverse liver reactions

PATIENTS AND METHODS

vomen 20 30 35 and 68 years of age had been dly treated with sulfonamides as well as other because of recurrent urinary tract infections In f previous experience of adverse liver reactions in ation with sulfonamides treatment with this drug nitiated in three cases once and in one case twice New attacks of jaundice occurred on all five occasion The prepartion concerned was on all occasions Sulfa pral®—a combination of sulfamethizole and sulfamethoxy pyridazine which has been widely used in Scandinavia during several years for treatment of urinary tract infections—in a standard dose of 2 tablets twice daily The period of treatment before onset of jaundice was 2–9 weeks at their first attack of jaundice and 1 2 weeks at their second attack (Table I) The patients had received 2–4 courses of sulfonamide treatment previous to that *during which jaundice first appeared*

Liver function tests were performed by standard techniques as described elsewhere (6) Liver biopsies were obtained by a modified Menghini technique The histological alterations were classified according to suggestions by an international group (1) Presence of hepatitis B surface antigen in serum was analysed with a radioimmunoassay (Ausria II Abbot Laboratories) and anti HBs was determined by Ausab (Abbot Laboratories)

RESULTS

The first attack of jaundice appeared during the third fourth and fifth period of sulfonamide treatment respectively (Table I) The period of treatment before onset of jaundice was shorter during the second (mean 1 5 weeks) and third (mean 1 week) attacks than during the first (mean 5 weeks)

The initial symptoms during each attack were fatigue nausea vomiting and fever followed by dark urine and jaundice The maximal levels of serum bilirubin alkaline phosphatases and SGPT are shown in Table I As a rule high serum levels were rapidly reached after re-exposure to the drug The duration of abnormal aminotransferase levels was 4–12 weeks (mean 7 7) Alkaline phosphatase levels were moderately raised on all occasions but had no correlation to histological alterations of bile stasis In all four patients the galactose tolerance test showed a normal half life of galactose (9–14 min) at about the time when the aminotransferase levels had returned to normal

Table I *Maximal levels of serum bilirubin alkaline phosphatases and SGPT duration of ch... levels in serum and histological abnormalities in liver biopsies*

Case no	Period of sulfonamide treatment	Duration of treatment before appearance of jaundice (weeks)	Maximal level of Serum bilirubin (mg/ml)	Alkaline phosphatases (Buch units)	SGPT (IU)	Duration of abnormal SGPT levels (weeks)	Liver histology
1	4	6	31 8	11	1 180	12	Hepatitis-like rea...
	5	*2*	*15 9*	*10*	*1 830*	*10*	with bile stasis ...
	6	1	25 1	13	1 810	9	three occasions fibrosis at the ... attack
2	5	3	7 4	14	600	8	Hepatitis like ...
	6	2	9 2	12	1 540	4	and in add... eosinophilia at ...
3	4	9	10 7	10	1 800	8	Hepatitis-like ...
	5	1	3.5	13	576	5	and in add... stasis at 1st ...
4	3	2	6 7	16	870	7	Hepatitis-like ...
	4	*1*	*3 0*	*15*	*570*	6	*biopsy not per...* during 2nd attack
Normal value			≤1 0	<8	<25		

A hepatitis like reaction with moderate or prominent parenchymal cell damage (single cell necrosis hydropic degeneration and ballooning) was seen in all liver biopsies Portal inflammatory infiltration with mononuclear cells and in one case eosinophilia was also observed A more or less apparent Kupffer cell reaction was present in all biopsies and in some cases signs of bile statis as well (Table I and Figs 1–3) The histological alterations during the second attack were as a rule not more prominent than during the first However discrete signs of chronicity with slight fibrosis were fo... cases during the second attack The p... had a third exposure and a third attack ... showed a more prominent fibrosis in the ... biopsy However the liver archite... altered

DISCUSSION

It has long been known that drug hypersensitivity reactions may also ind...

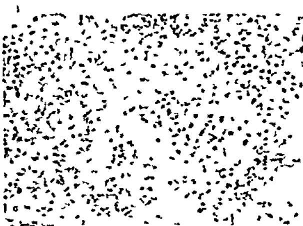
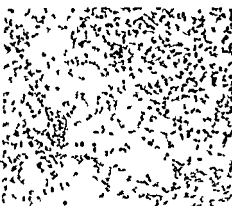



Fig 1 Case 3 First attack (*a*) Hepatitis-like picture with dissarray of the architecture inflammatory cell infiltration and Kupffer cell proliferation (×120) (*b*) Parenchymal cell damage with hydropic degeneration and ba... multinuclear hepatocytes are visible (×2...



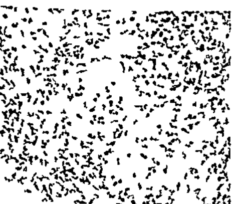


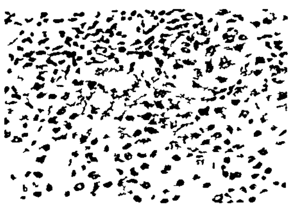
ase 3 Second attack (*a*) In princ ple the same is at the f rst attack (×1?0) (*b*) Pronounced lular damage with s ngle cell necros s (×2?0)

actions (7) Th s type of liver damage has ggested to occur with a frequency of 0 01) The true inc dence is not known because nos s s d ff cult to verify It has so far been ble in most cases to dist nguish th s type of act on from viral hepat t s Now when cal methods for different ating hepat t s A at t s B from other types of hepat tis are e th s d ff culty is at least partly overcome rimary attacks of jaund ce in our four pa ere all diagnosed as viral hepat t s When xt ep sode of jaund ce occurred after stration of the same sulfonamide prepara 'as understood that also the f rst attack was y assoc ated w th sulfonam de treatment

The patients were all HBsAg negat ve during their attacks of jaund ce and d d not develop anti HBs during convalescence No test for hepat t s A v rus was ava lable at the t me when these ca es were diagnosed (n 1971 75) However there was no hepatit s contact fore gn travel or other factor speak ng in favour of hepat t s A nfect on

Different histological abnormal t es have been reported in associat on with sulfonam de nduced l ver react ons In most cases areas of hepatocel lular necros s w th inflammatory inf ltrat on and somet mes eos noph l a have been reported (?) The hepatocellular injury is in many cases accompan ed by cholestat c features Also a more chron c type of l ver damage has been described (8)





a e 4 Second attack (*a* *b*) Fa rly pronounced reac on with a tendency to septal prol fera *a* ×1 0 F g *b* ×220)

The liver biopsies of all our four patients have shown signs of hepatocellular damage with mono nuclear inflammatory reaction and cholestasis has been seen in six b opsies We have called this a hepatitis like reaction Signs of a more chronic process have been slight with some fibrosis but no picture of chronic aggressive hepatitis

Repeated exposure to a drug entails a greater risk of sensitization and this is a major problem in patients with recurrent urinary tract infections They are as a rule exposed to several drugs on repeated occasions Once sensitized the patient may react vigorously also after a small challenging dose Thus the benefits of establishing a correct diagnosis must be weighed against the potential harm of a provocative exposure

Besides the allergic type of liver reaction a direct toxic effect of sulfonamides has been assumed to contribute to the liver damage However the present cases as well as others reported in the literature seem to favour the hypothesis of a mechanism of *acquired hypersensitivity (2 3) The occurrence of* a latent period between the beginning of administration of the drug and the development of the clinical manifestations of hepatic injury strongly favour the hypersensitivity theory Further this type of liver damage does not seem to be dose-dependent which might be expected for a pure toxic liver reaction

Pre-existing liver damage is not considered a contraindication to the use of sulfon... liver reaction has once occurred ... treatment (and challenge) should b... Awareness of potential sensitiza... and recognition of its cl nical man... continuing importance

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Streptozotocin Treatment of a Pancreatic Tumour Producing VIP and Gastrin Associated with Verner-Morrison Syndrome

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ACT A 57 year-old male patient with -izing non beta islet cell carcinoma of the -s is described Both gastrin and VIP levels evated and the patient suffered from a -e of pancreatic cholera and hyperacidity -our contained gastrin and VIP as demon by immunofluorescence The patient also had y of familial renal stone formation and para nodular hyperplasia Resection of pancreatic in 1973 resulted in four years without symp n 1977 definite signs of multiple hepatic appeared These signs disappeared after -otocin given in a dosage of 2 g three times at intervals The patient has remained well for ths after this treatment The causative agents linical syndrome in this case are discussed in circulating hormone levels

-rds Verner Morrison syndrome VIP gastrin -otoc n treatment

-d Scand 206 223 1979

-ndrome of watery d arrhoea hypokalaemia -hlorhydria (WDHA syndrome pancreatic or Verner Morrison syndrome) associated -n beta islet cell tumour of the pancreas was scribed by Verner and Morrison in 1958 (24) gh most of the cases are associated with atic tumours the syndrom can be pro- by various tumour types (20) The causative) is still not firmly established although the -t presence of increased plasma and tumour -tration of vasoactive intestinal polypeptide 2 20) a 28 amino acid peptide (21) known to the symptoms seen in this syndrome favour -le of VIP In some patients however the hormonal overproduction involves more than one humoral agent A few cases have been reported in wh ch the responsible agent is suppose l to be pancreatic polypeptide (PP) (13) or prostagland n E (9)

Streptozotocin an antitumour antibiotic has re cently been used successfully in the treatment of the WDHA syndrome (6 11 22) In this report we describe successful streptozotocin treatment of a patient with a pancreatic carcinoma producing both VIP and gastrin

CASE REPORT

A male born in 1910 was surg cally explored in 1969 because of renal stones and severe hypercalcaem a (S Ca >3 0 mmol/l) Two macroscop cally normal parathyroids were left intact and one macroscop cally enlarged para thyro d was removed Morpholog cally th s demonstrated a nodular hyperplasia cons st ng partly of oxyph l c cells partly of ch ef cells S-Ca returned to normal after opera tion His father and two brothers one of whom had been operated on for parathyro d hyperplasia had had recur rent renal stones

In Nov 1972 the pat ent compla ned of recurrent short ep sodes of watery d arrhoea s nce July The S Ca was normal at th s t me In Dec a gastric ulcer was diagnosed which healed on conservat ve med cal treatment S-Ca was st ll normal In June 1973 he became acutely ill and was readmitted to Malmo General Hospital with abdomi nal pains and large watery d arrhoeas 9–10 times daily Laboratory tests revealed severe dehydrat on hyper calcaem a and hypokalaemia H s general cond t on

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Abbrev at ons WDHA syndrome the syndrome of wat ery diarrhoea hypokalaemia and achlorhydria VIP vasoact ve intest nal polypept de PP = pancreatic polypept de ZE syndrome = Zoll nger Ell son syndrome

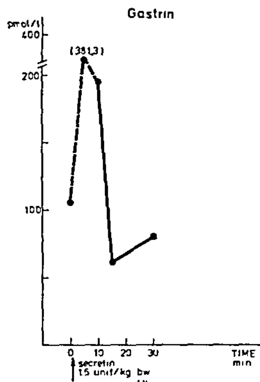


Fig 1 Serum gastrin after administration of secretin as a bolus injection

deteriorated in spite of i v fluid supplements The stool volume varied between 5 and 8 l per day In the Intensive Care Unit the patient required respiratory assistance and approximately 10 l of fluid intravenously including 200–400 mmol of potassium daily The fasting secretion of hydrochloric acid was very high and a large duodenal ulcer was found

Anghiography of the coeliac artery yielded a large part ly calcified tumour in the pancreatic tail On laparotomy in uly 1973 a partial resection of the pancreas was per ed There were no macroscopical metastases in the ver or the other abdominal organs Morphologically the sected part of the pancreas contained three separate non beta islet cell carcinomas Immunofluorescent studies demonstrated a positive reaction with antibodies to VIP and gastrin Postoperatively the patient recovered completely clinically

The patient remained well but slightly hypercalcaemic until March 1977 At that time the diarrhoeas recurred rather abruptly He was admitted in early April with four or five diarrhoeas daily and had at that time experienced a weight loss of 6 kg He deteriorated rapidly after admission Multiple liver metastases were visualized on scintigraphy and angiography

He was referred to the Medical Department University Hospital Uppsala in May 1977 At that time stool volumes varied between 2 and 9 l daily The basal gastric acid output was low (0 μmol/min) and after pentagastrin stimulation 136 μmol/min (normal response) X rays of the sella turcica and lungs as well as computer tomography of the skull were normal

The patient was initially trea ed with [illegible] electrolytes (potassium 80–1?0 mEq [illegible] fluids (4–6 l/d) Thereafter a course of [illegible] given intravenously in three doses of [illegible] of one week Already after two doses [illegible] formed stool daily

Three months later he had gained 7 kg [illegible] laboratory test values had become norma[illegible] cept for PP and S-calcium

At reexamination 20 months after [illegible] ment the patient was quite well and ha[illegible] ordinary work Computer tomography of [illegible] and liver scintigraphy as well as labora[illegible] normal except for S-Ca which remained [illegible] and S-PTH which was elevated to 0.34 μg[illegible]

The patient fulfills the criteria of multip[illegible] adenomatosis type I with pancreatic tumo[illegible] plasia of parathyroids

LABORATORY METHODS

Routine haematological and serum anal[illegible] formed at the Laboratory of Clinical Che[illegible] sity Hospital Uppsala Gastrin PP VIP and [illegible] were determined by radioimmunoassay proc[illegible] 7 16)

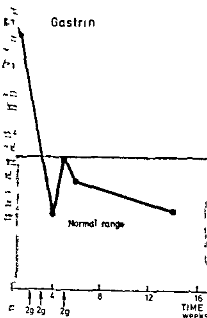
LABORATORY RESULTS

The laboratory findings before and af[illegible] treatment are summarized in Table I [illegible] gastrin PP and VIP levels were found [illegible] treatment

Because of hypergastrinaemia ea[illegible] of ventricular and duodenal ul ers [illegible] hyperacidity a secretin test was pe[illegible] shown in Fig 1 secretin injection cause[illegible]

Table I *Laboratory tests before and [illegible] after treatment with strepto otocin*

	Before	After
ESR (mm/h)	47	[illegible]
b-Hb (g/l)	96	[illegible]
S-albumin (g/l)	30	[illegible]
S-calcium (mmol/l)	2 ?4	[illegible]
S-phosphate (mmol/l)	0 8	[illegible]
S-potassium (mmol/l)	2 7	[illegible]
S-natrium (mmol/l)	140	[illegible]
fb-glucose (mmol/l)	5 0	[illegible]
S-gastrin (pmol/l)	114 7	[illegible]
S-PP (pg/ml)	866	[illegible]
p-VIP (pmol/l)	210	
p-somatostatin (pg/l)	78	[illegible]
S-PTH (μg/l)	0 37	[illegible]
S-calcitonin (pmol/l)	490	[illegible]



erum gastrin levels on different occasions during
ocin treatment

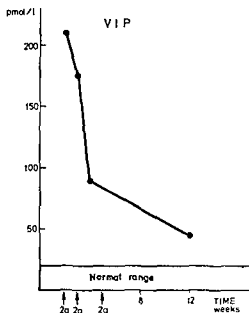


Fig 3 Plasma VIP levels on different occasions during streptozotocin treatment and three months after

d increase in serum gastrin concentration a e comparable to that seen in patients with r Ellison (ZE) syndrome

g the streptozotocin treatment gastrin and els decreased successively leading to a ation of serum gastrin concentration after two doses while the VIP level was still ely increased after the final treatment (Figs) PP levels however increased during it (Fig 4)

DISCUSSION

ndocrine tumours of the pancreas have the ty of multiple hormone production as shown munocytochemical investigations (12 18) h this multihormonal production might re difficulties it has also been stated clinical symptoms are often caused by duction of one hormone only (13)

present case the history of peptic ulcers viously demonstrated gastric hyperacidity t with hypergastrinaemia and a positive test suggest the presence of a gastrinoma ndrome) while the increased VIP levels and symptoms of watery diarrhoea and electro-balance favour the diagnosis of a VIPoma Morrison or WDHA syndrome) Only one case of bihormonal production of gastrin and VIP has to our knowledge been reported (10)

Streptozotocin treatment resulted in an immediate improvement of stool frequency accompanied by a normalization of circulating gastrin levels and a decline of VIP levels It could not however be stated whether the overproduction of gastrin and/or VIP caused the clinical symptoms of pancreatic cholera The differential diagnosis between the ZE syndrome and the Verner Morrison syndrome is often difficult since one third of the ZE patients have diarrhoea (4)

Earlier reports have demonstrated a beneficial effect of streptozotocin upon both VIP and gastrin producing tumours (6 22 23) in accordance with the present finding The increase in serum PP levels during streptozotocin treatment could possibly indicate an insensitivity of PP cells to streptozotocin This assumption agrees with findings in a previous report where no effect was seen after treatment of a patient with a PP producing tumour (15)

Our patient initially demonstrated elevated levels of serum calcitonin 480 pmol/l Following pentagastrin stimulation there was no further increase in the calcitonin levels After treatment with streptozotocin serum calcitonin returned to values within normal limits Hypercalcitoninaemia has

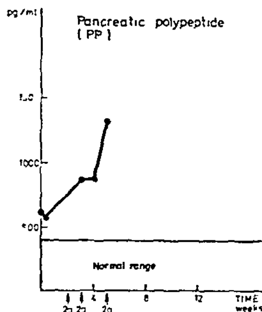


Fig 4 Serum levels of PP on different occasions during streptozotocin treatment

previously been reported in VIPomas (19) and in a variety of tumours including pancreatic non islet cell carcinoma (3) Hypercalcaemia has also been observed in connection with VIPomas and seems to occur in nearly half the patients with pancreatic cholera (17)

The mechanism causing hypercalcitoninaemia in our patient remains obscure Medullary carcinoma of the thyroid can be ruled out since there were no indications of this disease during the prolonged observation period Furthermore pentagastrin stimulation is known to cause increases in serum calcitonin in this condition (8) Hypercalcaemia per se was considered very unlikely since hypercalcaemia persisted whereas serum calcitonin became normal Glucagon a peptide structurally and pharmacologically related to VIP has been shown to release calcitonin in several animal species However his plasma glucagon levels were not elevated PP may also be ruled out since the levels of PP increased following treatment whereas calcitonin levels decreased Gastrin has also been connected with calcitonin release and this remains a distinct possibility If so the patient might be assumed to have had a long standing hypercalcitoninaemia causing hyperparathyroidism primarily of the secondary type followed by autonomous nodular hyperplasia (14) In case of hypercalcitoninaemia secondary to elevated circulating gastrin a pentagastrin stimulation is expected to cause a further increase in calcitonin However the hypercal[illegible] also be directly derived from the tum[illegible]

The present case illustrates the [illegible] hormone assay for the diagnosis and [illegible] of patients with chronic diarrhoea d[illegible] tumours Although streptozotocin [illegible] malignant non beta islet cell tu[illegible] pancreas has to be studied further [illegible] beneficial value in cases where other [illegible] alternatives are rather limited

ACKNOWLEDGEMENTS

Supported by grants from the Swedish Med[illegible] Council (project no 4534) and Astrid Ka[illegible]tion

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Acta Med Scand 206 229–231 1979

Changes ın Serum Trıglyceride and Cholesterol Levels during Long-Term Phenytoin Treatment for Epilepsy

P V Luoma M I Reunanen and E A Sotaniemi

rom the Clinical Research Unit Department of Internal Medicine and the Department of Neurolog University of Oulu Oulu Finland

ACT The effect of long term phenytoin on serum triglyceride and cholesterol levels tients with epilepsy was investigated In pa llowed up for six years, phenytoin treatment iciated with an increase in serum triglyceride lesterol levels The most significant increases evels were measured during the first months ipy whereafter values generally tended to The elevation in serum triglyceride con on was relatively greater than that in serum rol level Cholesterol concentrations how mained high for a longer period The results trate that phenytoin therapy for epilepsy is ed with a rise in serum triglyceride and rol levels, the degree of which seems to be to the duration of the treatment The changes ably reflect phenytoin effects on hepatic lipid lism

ds triglycerides cholesterol phenytoin epi

d Scand 206 229 1979

with drugs such as phenytoin or phe tal may alter liver function with an increase ictivity of the hepatic microsomal enzyme which is involved in the metabolism of itamins hormones and lipids (2 4 6 10 idies with these compounds have demon increases in serum lipid levels in healthy and patients with epilepsy (4 11) High triglyceride and cholesterol levels are con risk factors for cardiovascular diseases nce the follow up of serum lipid levels in cs undergoing anticonvulsant treatment was red important

present study was undertaken to evaluate the n by comparing serum lipid levels before and phenytoin treatment Serum triglyceride and erol levels in a group of epileptics some of have been followed up for six years are ed

PATIENTS

Twenty consecutive patients 9 men and 11 women n dergoing phenytoin treatment for epilepsy were inv ti gated The mean age of the males was 30 1 ye rs (range 19–59) and of the females 35 5 years (range 1?– Their serum triglyceride and cholesterol levels were de rmin d before the commencement of phenyto n treatment a u after one three and six months of therapy ar d th–n reg ularly at six month intervals

The patients live in the same area where dietar habits vary little The diagnosis of epilepsy was bas–d on case history and neurological findings The daily phenytoin dose was 200–350 mg The patients had no oth r regular drug treatment

METHODS

Blood samples for determination of serum triglyceride and cholesterol were drawn after an overnight fast S–rum lipid concentration was determined by standard au o-analyzer techniques (Technicon) The triglyceride assay used the method of Wahlefeld (14) and serum cholesterol assay the method of Huang et al (7)

Student s *t* test for paired data was employed to calcu late the significance of the results In each patient lipid values during therapy were compared with their own val ues before treatment

RESULTS

Phenytoin therapy was associated with a significant gradual increase in serum triglyceride level (Table I Fig 1) During the first month of therapy triglycerides increased by 25% The highest mean concentration measured three months after com mencement of the therapy At that time tri glycerides were 45% above the pretreatment lev el Later the values decreased and did not differ significantly from the mean pretreatment values Before treatment four (20%) of the 20 patients had triglyceride concentrations of over 1 6 mmoles/l After one and three months of therapy eight (40%) and seven (35%) patients respectively had high serum triglyceride levels

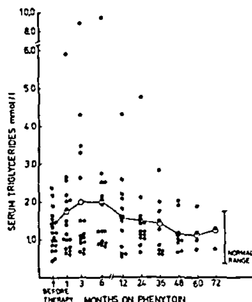


Fig 1 Individual (●) and mean (O) serum triglyceride values before and during phenytoin treatment

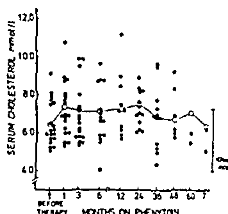


Fig 2 Individual (●) and mean (O) serum c[illegible] values before and during phenytoin treatme[illegible]

There was a significant increase also in serum cholesterol concentration during phenytoin therapy (Table I Fig 2) The increase during the first month was 14% and the values remained at this high level for two years Serum cholesterol values exceeding 7 5 mmoles/l were found in four patients before treatment and in nine and six patients after treatment for one and three months respectively

DISCUSSION

Elevated serum cholesterol levels have been dem[illegible] [illegible]d in epileptics undergoing anticonvulsant [illegible] (1 11) The present results show that therapy with phenytoin might be associated with temporary changes in serum triglyceride and cholesterol levels In epileptics followed [illegible] years there was an increase in serum tr[illegible] and cholesterol levels during the first [illegible] therapy after which the values in [illegible] tended to decrease The rise in serum tr[illegible] concentration was relatively greater th[illegible] crease in serum cholesterol level Ch[illegible] however remained elevated for a lo[illegible] Lipid values measured later did not d[illegible] treatment levels This suggests that th[illegible] serum lipid levels in phenytoin treated s[illegible] be considered an adaptation phenome[illegible] the use of the drug

The mechanism by which serum lipid[illegible] in phenytoin treated subjects is not [illegible] changes observed however may be [illegible] drug effects on liver function and alter[illegible] fate of endogenous substances affecting l[illegible] ics The liver has a central role in the [illegible] serum lipids Therapy with compounds

Table I *Serum triglyceride and cholesterol levels (mmoles/l) before and during phenytoin (PH) [illegible] for epilepsy*

	Before PH	Duration of PH treatment (mo)							
		1	3	6	12	24	36	48	[illegible]
Triglycerides									
Mean	1 39	1 76***	1 99	1 96	1 55	1 48	1 39	1 11	[illegible]
S D	0 96	1 24	1 97	2 06	1 01	1 07	0 96	0 51	[illegible]
Cholesterol									
Mean	6 41	7 30 **	7 14***	7 12	7 23**	7 64*	6 67	6 [illegible]	[illegible]
S D	1 17	1 45	1 88	1 69	1 54	1 47	1 71	1 [illegible]	[illegible]
n	20	20	20	17	14	14	12	9	4

$^*p<0.05$ $^{**}p<0.01$ $^{***}p<0.005$

n and phenobarbital may affect liver func l cause prol ferat on of hepatic endoplasm c m Th s phenomenon may be associated ered b le ac d lip d and hormone metabo- 4 10 1? 13)

to n treatment l ke phenobarb tal therapy y facil tate the absorption of l pid precursors ulat ng hepat c bile acid synthesis and bile he rate of triglyceride synthesis in the liver ther be regulated by the activity of the en of the triacylglycerol pathway in which *atidate phosphohydrolase is the rate l miting* (5) Phenyto n may stimulate phosphatidate ohydrolase and thus enhance triglyceride on in hepatocytes Stimulation of apolipo- synthesis in connection with enzyme in could further facil tate the output of the *nd contribute to the elevation of lipid levels* n

increase in serum cholesterol in phenytoin subjects may reflect drug induced increases it c m crosomal 3 hydroxy 3 methylglutaryl eductase activity which is the rate limiting *cholesterol b osynthesis (13) Phenobarb tal* nt has been shown to increase the activity of zyme n liver biopsy samples (3)

di t on to the d rect effects on the enzymes of d synthes s pathway phenytoin can alter the s of endogenous substances such as insulin *ro d hormones which can affect serum lip d* Phenyto n can inhibit insulin secretion (8) so decrease serum thyroid hormone levels hich m ght be reflected as a rise in serum vels

rapy with phenytoin increased the frequency ated triglyceride and cholesterol values The se in triglyceride level was in some cases very but also more short lived than the change in terol concentration The increase in serum terol level may therefore be more closely re o the enzyme induction phenomenon than the in serum triglyceride *concentration*

ACKNOWLEDGEMENT

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BOOK REVIEWS

Arterial hypertension WHO Technical Report Series no 628 58 pages Sw fr 6 – WHO Geneva 1978

The WHO series of technical reports also contains a small number of monographs on various interesting clinical topics The list of the last numbers 590–630 is quite impressive and represents a reference library of great importance for many branches of medicine There is one possible drawback with this type of publication the fact that this is a world organization leads to the inclusion of experts selected from as many different countries as possible In spite of this the standard of the majority of the experts usually is surprisingly good

Two of the last reports are of great interest to the internist No 628 treats one of the greatest and most acute problems in internal medicine namely the classification epidemiology and management of hypertension as well as attempts at control of this disease in the population There is also an "annex" treating antihypertensive agents

The fact that Professor Gross from Heidelberg has been the chairman is of course a guarantee that the therapeutic side of the problem is well represented I regard it as a *rather serious deficiency that so few references are given* The overwhelming abundance of publications in this field makes it imperative to have a well selected list of publications for reference

The readers of the Acta Medica Scandinavica will note with satisfaction that the Scandinavian investigator Wilhelmsen from Gothenburg has been one of the experts

Jan G Waldenström

Immunodeficiency WHO Technical Report Series no 630 73 pages Sw fr 7 – WHO Geneva 1978

Immunodeficiency is a puzzling condition especially when it has a genetic background The fact that many must be involved in the production of immunoglobu molecules makes it hard to understand how one point on could explain a general decline in the synthesis of a great many different immunoglobulins The recent findings that the basis may be a mutation in the genes that control the synthesis of one specific enzyme such as adenosine diaminase (ADA) and purine nucleoside phosphorylase (PNP) is easier to understand These enzymes are obviously necessary for the development of the cells that are involved in immunoglobulin synthesis These very important facts have only been mentioned very briefly

Table I contains a rather formidable list of primary specific immunodeficiencies The number is 17 but no 1 contains five subgroups and no 17 two thus 22 in all The reader misses references to all the lists of "different processes that are listed in Tables 1 2 and 3 To the reviewer it seems clear that a number of these conditions will disappear as independent individuals and possibly others will be added

On the whole this brief monograph contains a wealth of facts There is little room for discussion of problems but as a skeleton containing main facts it see very valuable The discussion of therape competent

The price is obviously very favourable is strongly recommended to the student or t needs an overview of the field in its presen

Jan G

The endocrine function of the human a Edited by V T H James M Serio G Martini 612 (628) pages £19.50 Academ and New York 1978

This volume is a record of the papers p Serono Symposium held in Florence in Oc tains 36 contributions ranging from stero and regulation of the adrenal cortex t docrinology The clinical part includes no sical disorders such as hypercorticism dosteronism and congenital adrenal hy also discussions on hirsutism and hyperte of the Symposium was to provide a picture of current views and research on a function" This intention has certainly

It is impossible to review all the volume of this type Since the scope is reviewer will also be biassed by his own topic However it must be stated that th whole is excellent It provides inter throughout and it will also serve as a ref which most libraries would benefit from

The papers dealing with steroid biosynthe tion are very thorough and even include monoaminergic fibres and prostaglandins havioural effects Protein binding of stero variations of steroids as well as binding pr sented Both these sections are very good good frame for futuristic outlooks

Congenital adrenal hyperplasia and hir dated and the discussion on hirsutism is triguing Hypertension with an emphasis o of various steroids is discussed in depth retaining properties of aldosterone and th primary aldosteronism are well present angiotensin system and its effect on the complement presentations of the role of v and the arenal cortex in hypertension saralasin and the interpretation of such dat in an excellent way

Finally the adrenal function in the fet infancy and puberty is presented with a ver of the clinical disorders at the time of puber

This volume can certainly be recommend me great pleasure to give all the contributor excellent piece of work I can only wish th participated

John Fredrik Dymling Mal

Acta Med Scand 206 233–237 1979

Immune Complex Glomerulonephrıtıs ın Chronıc Granulomatous Dısease

Case Report ı f an Eıgl teen Year Old G rl

D J van Rhenen M I Koolen Th M Feltkamp-Vroom and R S Weenıng

the Department of Med c ne Academ sch Z ekenhu s der Vrıje Un ers te t the Depa tment of Pa naart Z ekenhu s the Ped atric Cl n c B nnen Gastl s and the Cen ral Laboraton of the Ne he l nd Red Cross Blood Transf s on Sen ce Amsterdan Tl e Ne herlands

ACT An 18-year-old gırl ıs descrıbed who ed advanced renal sclerotıc lesıons probably d by local focal glomerulonephrıtıs which d w th a Staphylococcus aureus abscess It ıs ssıed that ımmune complex glomerulone developed provoked by long term antıgenıc tıon of Staphylococcus aureus The cause of ng term bacterıal ınfectıons was a defect of gocyt c cells to kıll bacterıa effectıvely a dısnown as *chronıc granulomatous dısease* ry w th ıntracellularly actıve antımıcrobıal red the renal functıon tıll no more s was necessary

rds chron c granulomatous dısease cırculatıng *complexes local focal* glomerulonephrıt s ın larly actıve antımıcrob al agents

ed Scand 206 233 1979

currence of ımmune complex glomerulos has been descrıbed not only ın pat ents ıbacute bacterıal endocard tıs but also ın pa w th other serıous ınfectıons (3 7 11) We a pat ent who as a result of a dısturbance n ıct on of her polymorphonuclear leukocytes has been exposed to Staphylococcus au fect on for a long perıod Subsequently she ped an ımmune complex glomerulonephrıtıs dysfunct on of PMN known as chron c ımatous d sease (CGD) ran a very unusual because of the pat ent s late age at onset

CASE REPORT

ear-old gırl w th rap dly progress ve renal faılure mı tted to our hosp tal *for the first tıme* n *May 1977* the fırst ch ld of healthy non-consangu neous par 15-year-old s ster and a 9-year-old brother are healthy The pat ent had felt phys cally we n y 4 when she was adm tted to a hosp al el ewhe a e slowly resolv ng pneumon a of tl e r gh uppr be No bacterıa could be solated F brot c s ars we eer af *wards ın the top of the rıght lung Hepa osp e me a* was found durıng th s adm s on In Feb 1976 he I compla ned of pa n n the rıght upper abd men In M 1976 she was adm tted w h se ere abdom ra pl n Operat on d sclosed an overwhelm ng perıtor au d by perforat on of a lıver abscess Staphylococ *was ısolated from the pus Mıcroscopıc hema r a* reported already at th s t me (Table I)

In Jan 1977 she was readm tted because hepa t w suspected wh ch could not be conf rmed Howe er m erythrocytes prote n and hyal n casts were found n urıne serum creatın ne was 106 μmol/l No d agnos s w *made nor was any treatment g ven In Aprıl 1977 she wa* adm tted aga n for severe abdom nal paın S nce her renal funct on deterıorated rap dly w th n two weeks she was transferred to our hosp tal

On adm ss on the pat ent looked gravely ıll and her temperature was 38 5 C Phys cal exam nat on revealed a *palpable mass ın the rıght upper abdomen* poss bly con nected w th the l ver Sk n pathology was not observed

Laboratory data

ESR 81 mm/h WBC 11 5×10⁹/l w th 79% morphologıcally normal PMN 18% lymphocytes and 3% bands Serum creatınıne had qu ckly rısen from 150 to 539 μmol/l Blood urea 21 4 mmol/l serum proteın 87 g/l with 39 4 g/l albumen and 23 6 g/l gammaglobul n Serum ımmune electrophoresıs showed no paraproteın Lıver funct ons (a o alkal ne phosphatase) were normal

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Abbre a ons ANF ant nuclear factor AU ant body un ts (Standard Hoechst Behrıng Werke) CGD chron c granulomatous d sease ESR erythrocyte sedımentat on rate PAS perıod c ac d Schıff PMN polymorphonuclear leucocytes WBC wh te blood cells

Correspondence address D J van Rhenen Academısch Zıekenhu s der Vrıje Unıvers te t de Boelelaan 1117 Amsterdam The Netherlands

Table I *Summary of laboratory and clinical findings*

Date	Serum creatinine (μmol/l)	Urine sediment	Urinary protein (g/l)	Anti staphylo-lysine titer (AU)	Details
May 1976	108	Erythrocytes	?		Peritonitis
Jan 1977	154	Many erythro-cytes casts	++		Hepatitis
April 1977	150	Many erythro-cytes casts	++		Deterioration of renal function
May 1977	539	Many erythro-cytes casts	2 1	100	Admission to our hospital first skin biopsy haemodialysis, surgical abscess drainage PMN functional analysis Therapy 80 mg trimethoprim + 400 mg sulfamethoxazole daily
July 1977	Haemo-dialysis	Few erythro-cytes casts	2 2	1	Surgical renal biopsy second skin biopsy
Dec 1977	239	Few erythrocytes	1 9		End of haemodialysis PMN function analysis
April 1978	308	Few erythrocytes	1 8	1	Relapse third skin biopsy circulating immune complexes demonstrated Therapy rifampycine 600 mg daily
June 1978	254	Few erythrocytes	1 2		Fourth skin biopsy

Many leucocytes erythrocytes granular and hyalin casts were seen in the urine sediment urinary protein was 2 1 g/l No morphological abnormalities were observed by i v pyelography Liver scintigraphy and echoscopy suggested an intrahepatic process

The most probable diagnosis was a recurrence of the liver abscess with Staphylococcus aureus and the development of immune complex glomerulonephritis For confirmation of these possibilities the following investigations were performed Antistaphylolysine titer 100 AU (normal value <0 5) Complement CH_{50} 86 U/ml (lower normal limit 50) No indications for diffuse intravascular coagulation were found ANF negative Latex fixation test positive Immunoelectrophoresis of the urine showed an aselective proteinuria

A summary of the laboratory and clinical findings is given in Table I

Histo and immunopathological investigations

Skin biopsies The first punch biopsy was taken from the normal skin of the extensor side of the forearm one day after admission Immunofluorescence studies revealed fine granular material in the capillary walls of the papillary dermis positive for IgA and fibrinogen less extensively also for IgM and C 3/4 The second biopsy taken two months after admission revealed no deposits The third biopsy taken during relapse showed granular material in the capillary walls of papillary dermis positive for IgM IgG and C 3/4 Clq was not found The fourth biopsy showed no abnormalities The skin biopsies were studied by Dr C Nieboer Department of Dermatology AZVU

Surgical renal biopsy (performed two months after admission because of the patient s poor condition) The renal biopsy was divided in two parts one for fi- other for freezing in liquid nitrogen The fixed t routinely embedded in paraplast cut and sta haematoxylin and eosin periodic acid silver me- and periodic acid Schiff (PAS) The frozen tissue in a cryostat and studied for the presence of Ig IgM IgE fibrinogen Clq and C3

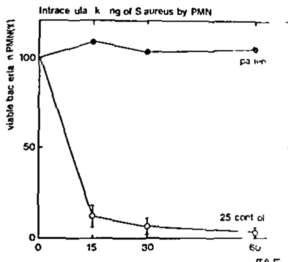
By light microscopy 16 of the 30 glomeruli showed moderate to advanced sclerosis (Fig 1) 10 of the 30 glomeruli showed definite local foci with lobular condensation capsular adhesions cent formation (Fig 2) About 5 glomeruli normal with only slight endothelial swelling The



Fig 1 PASM/Azan stain showing glomerulus vanced sclerosis



Fig S s ain show ng glomeruli w th capsular adhe ...cent format on and sclerosis



F g 3 Intracellular k ll ng capa ty by pol r orp onu clear leukocytes (mean ± S D)

... was increased locally due to fibrosis and/or ... by lymphocytes and h st ocytes Tubuli w th ...atures were seen in the fibrot c areas and fre ...lar casts n the medulla

...fluo escence revealed no depos ts of immuno ... n the glomerul Some patchy ... and C3 were present in the walls of the small ...e casts contained IgA

...gnos s was advanced renal sclerot c les ons ... local focal glomerulonephrit s

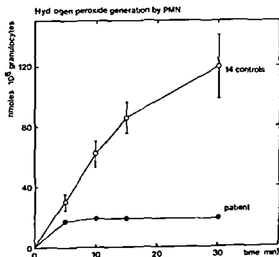
...l capac es of phagocyt c cells

...efects in res stance against bacterial infect ons ...c ed funct onal tests were performed on PMN ...cytes Studying the funct onal capac t es of the ... found a normal chemotact c respons veness as ... w th the lead ng front method (16) and case n ...tractant 65 μm (mean + S D in 31 normal ...1+5) The uptake of C labelled Staphylococ... ...s was measured essentially as described by ... (14) In this assay lysostaphin is used to lyse ...and o her non phagocytized bacteria The pa... ...N phagocytized these bacteria even better— ...he bacteria ngested per PMN per m n—than ...ntrol cells 1 14+0 34% (mean ± S D n=?0) ... the pat ent s PMN were unable to k ll these ...bacteria w thin 60 m n as judged by an assay as described by Solberg (13) (Fig 3)

...use of th s defect in intracellular k ll ng was the ...f stimulat on of the ox dat ve react ons known ...ital importance for the k ll ng of bacteria During ...ps s a 20-fold ncrease n oxygen consumpt on is ...observed (15) The consumed oxygen s re... ...obably by an NADPH ox dase to superoxide ...1) These rad cals d smute spontaneously or by superox de d smutase to hydrogen perox de ... bacteric dal propert es

...ent s PMN however failed to show the normal ...y burst Oxygen consumption 0 3 nmoles O_2/ ...min was hardly stimulated during phagocytos s ...S D in 20 normal controls 4 2+1 3) As a result no st mulat on of superox de rad cal pro u on o shown) and hydrogen perox de format on 8 a ob- served (F g 4) These abnormal t es were con r d two occas ons Moreover the monocytes a so f o produce hydrogen perox de during inges on of z mo n (not shown) Activit es of the enzymes g u o 6 phosphate dehydrogenase 6-phospho-glucona e d h d genase glutath one perox dase and glutath on redu tase n the PMN were all normal

We concluded therefore that th s pat ent suffe ed from CGD Fam ly stud es failed to detect carriers of th s d s ease a normal f nd ng n female CGD pat ents (9)



F g 4 Hydrogen perox de generat on by polymorphonu clear leukocytes (mean + S D)

Table 1 *Reported cases of gangrene of the tongue in temporal arteritis*

	Age (y)	Sex	Histological examination
Bergan (1) (Horton (10))	80	♀	Not performed
Howard & Cremin (11) (Wise (18))	74	♀	Not performed
Brearley & MacDonald (3)	82	♀	Arteritis temporalis
McGill (13)	77	♀	No information
Pitt et al (14)	78	♀	Organized thrombosis without giant cells
Reed & Inglis (16) (Horton (10))	72	♀	No information
Kinmont & McCallum (12)			
Davis & Davis (4)	81	♀	Giant cell arteritis
Present study	69	♀	Arteritis temporalis (giant cell arteritis)

Horton (10) did not observe any case of gangrene among his 200 patients Kinmont and McCallum (12) reported that 7 of their 59 patients with giant cell arteritis had varying degrees of glossitis rarely followed by gangrene That gangrene of the tongue is so rare may be due to the rich blood supply with anastomoses of the artery branches whereas the frequent ocular involvement in temporal arteritis (2) probably is due to the fact that the retinal artery is an end artery Gangrene of the tongue has been reported in at least 9 patients with suspected or histologically verified temporal arteritis (Table 1) Pain in the jaw muscles (10) and even the tongue (8) is often seen and may be explained by reduction of blood supply in the acute stage of the disease

As the necroses indicate a bilateral arterial involvement it seems unlikely that the unilateral mechanical intervention (arterial biopsy in local anesthesia) might have precipitated the symptoms On the other hand manipulation of the artery may have resulted in retrograde spasm or thrombosis caused a reduction of the blood flow to a level low the critical resulting in ischemic necroses Progression of symptoms after biopsy has not been described in the literature but Profant (15) reported progression of symptoms after extraction of teeth

Negative biopsies are rather frequent (17) In these cases the diagnoses of temporal arteritis or polymyalgia rheumatica are based on clinical symptoms and blood tests, and corticosteroid treatment is started It is agreed that immediate steroid treatment is indicated in case of eye involvement (2) To avoid further progression and such sudden complications as the above mentioned we would like to suggest that all patients should be treated with steroids before biopsy if they are strongly suspected of having temporal arteritis or polymyalgia rheumatica The possibility of obtaining a positive biopsy during or after steroid t[...] does not seem to be diminished by this p[...] (5 6)

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...ug Induced Neutropenias in the Stockholm Region 1976–1977

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...ACT Previously we reviewed the incidence ...es of drug induced neutropenia in the Stock...gion during the years 1973–75 We here pre... equivalent study for the years 1976–77 The ...incidence of drug induced neutropenia cy...es excluded remained around 0 01 ... About ... of the cases were caused by sulphonamides ... the other causes antithyroid drugs and ...lazines were most frequent The mortality ... 27% in contrast to only 2% in our previous ...f the seven patients who died 5 had taken ...amides

...s agranulocytosis drugs—adverse reactions
...d Scand 206 241 1979

...vious paper we reviewed the incidence and ... of drug induced neutropenia in the Stock...gion between 1973 and 1975 (1) We also ...hat only approximately 40% of the cases ...n reported to the Swedish Adverse Drug ...n Committee Due to this fact and also be...ew drugs are introduced continuously we ...t important to undertake regular follow up ... We present a study comprising the Stock...gion during the years 1976 and 1977

METHODS

The methods have been detailed prev... records of patients discharged with ... agranulocytosis (1967 ICD classification ...99 ... the years 1976–1977 were obtained from the S...kh... County Council Public Health Board Information S...tem The records were reviewed for the pre...e of neutropenia (reflected as blood neutrophil ...un $<1.0\times10^9/l$) duration of hospital stay sex and age of the patient intake of drugs preceding the de...t...n o... neutropenia other possible co-existing disease... and clinical presentation of infections and the general out...me

Neutropenia was classified as drug induced ... known to cause neutropenia had been taken ... followed its withdrawal (the patient surviving ... phase) and no other diseases associated with neut...en... were present

Drug induced neutropenias were further d...ded ... three groups depending on whether the patients had taken only one drug (group I) more than one probable drug (group II) or drugs causing a dose-dependent neutropen... (cytostatics) The latter group is not considered in the following discussion

RESULTS

During the years 1976–77 93 patients had been discharged with the diagnosis of agranulocytosis The records of three patients were not found Eight pa...

... Additional data on the 27 cases of drug induced neutropenia (groups I+II)

...ent counted as one in the sum was admitted once in 1976 and once in 1977 because of chronic neutropenia ... to be caused by penicillamine

No of cases	Days of hospital stay (mean)	Males N	Males Age (y) Mean	Males Age (y) Range	Females N	Females Age (y) Mean	Females Age (y) Range	Fatal cases
16	12 6	4	45 5	8–68	12	50 9	17–68	3
12	12 5	5	71 8	51–83	7	66 0	48–76	4
27	12 6	9	61 2	8–83	18	56 5	17 76	7

Table II *Drugs involved in 27 cases of drug induced neutropenia Fatal cases are given in parentheses*

Group I=patients who had taken only one drug group II=patients who had taken two or more drugs (all possible neutropenia-causing drugs being listed) Swedish synonyms at present on the market are given in parentheses

	Group I	Group II
Sulphonamides	11	2
Various	9 (3)	1
Salicylazosulfapyridine (Salazopyrin®)		
Trimethoprim-sulfamethoxazole (Bactrim® Eusaprim® Trimetoprimsulfa®)		1 (1)ᶜ
Antithyroid drugs	2	
Propylthiouracil (Tiotil®)	1	
Thiamazole (Thacapzol®)	*1*	
Phenothiazines	1	2
Unspecified	1 (1)	
Trifluoperazine (Terfluzin®)		1
Chlorpromazine (Hibernal® Largactil® Klorpromex®)		1 (1)ᶜ
Diuretics	1	
Hydrochlorothiazide (Dichlotride® Esidrex® Dopamet comp® Hydromet® Moduretic®)	1	
Antibiotics		3
Amoxicillin (Imacillin® Bristamox®)		1
Ampicillin (Doktacillin® Pentrexyl®)		1 (1)
Gentamicin (Garamycina®)		1 (1)
Antiphlogistics	1	
Indomethacin (Indomee® *Confortid®)*	*1*	
Miscellaneous	6	6
Unspecified Italian purgative	1	
Penicillamine* (Cuprimine® Penicillamine®)	1	
Phenytoin (Diphydan® Epanutin® nantoin® Lehydan®)	2	
ipramin (Anafranil®)		1
n dine (Cardioquin® Kinidin® inytal®)		1
letamizole (Noramidopyrin)	1	
Tolbutamide (Artosin® Rastinon®)	1	
Phenemal (Included in 15 different pharmaceutical specialties on the Swedish market)		1
Chlormezanon (Lobac® Trancopal® Trancoprin®)		1
Paracetamol (Included in 17 different pharmaceutical specialties)		1
Multiple drugs*		1

The patient has a chronic neutropenia thought to be caused by penicillamine

* The patient had got at least 18 different drugs Many of them can cause neutropenia

ᶜ The patient had taken 4 possible drugs

Table III *Infections noted in the reco*
Some patients had signs of more than one t

	\
Septicaemia	4
Tonsillitis pharyngitis (necrotizing tonsillitis 1)	10
Pneumonia	3
Gastroenteritis	2
Miscellaneous	4
Fever of unknown origin	5
No signs of infection	5

tients did not fulfil the criterion of hav 1×10⁹ neutrophils/l Of the remaining 25 had *neutropenia caused by drugs* the above mentioned definitions Of th one has had 2 episodes of neutropeni different durgs and is therefore cou cases in the calculation of incidence t episodes altogether In addition to thes *one patient has a chronic neutropenia* to be caused by penicillamine She is our earlier paper (1) and does not rep case

Of the other 56 cases 23 were cau statics 12 were due to a primary haer ease and 11 to some other disease It could not be decided whether the neu due to drug or disease In 9 cases the neutropenia remained unknown

Based on the 26 new episodes of c neutropenia presented here the mean dence during these two years is esti 0 009% *(approximately 1 500 000 inhal* Stockholm region) Seven (27%) of th died of complications to the neutropeni

Table I gives further characteristics induced cases Table II lists the vario volved and Table III the infections des *records*

DISCUSSION

The pattern of drugs causing neu op study resembles earlier findings in most 2 3 4 6) Thus various sulphonamid thyroid drugs were among the most noted causes of drug induced neutroper

It is noteworthy that we still hav metamizole caused neutropenia althou

d awn from the Swedish market in 1973 ...nt w h metam zole neutropen a had taken t c drug bought abroad

...nnual inc dence of drug nduced neutro th s study (0 009%) s sim lar to that in ous study (0 01%) (1) These f gures are lar to the f nd ngs in earl er Swed sh om other parts of the country dur ng the .f of the 60s (2 4)

...iortal ty f gure of 27% closely resembles ...es of other nvest gat ons from recent years t s much h gher than the rate we found in ous study (?%) based on a 3 year survey r the reason for th s d screpancy it zes the potent ally serious nature of drug neutropen as

seven fatal cases five had taken sul des in one case together with other drugs Perhaps th s just reflects the wide ...se of sulphonam des The r use is expected ...ase further n the near future due to the t on of new sulphonam de-contain ng on p eparations One is trimetoprim ...toxazole (cotrimazole) Another is Fan s dar® (sulpha lox ne pyr meth m ne) h ch i now recommended by the WHO f r propl yl x aga nst chloroq n resistant mal r a (5 7) Il serum half l fe for sulph dox ne s al l q approximately 200 ho ırs wh ch hyp th et l could cause a prolonged and th s n ore s neutropen a

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Procainamide-Induced Lupus Erythematosus-like Syndrome in Relation to Acetylator Phenotype and Plasma Levels of Procainamide

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ACT To investigate the relationship between or phenotype and the development of pro- de (PA) induced systemic lupus erythema SLE like syndrome 28 patients with chronic ilar arrhythmias treated with PA were fol for one year The therapy was guided by monitoring in all patients in order to ob- e proposed therapeutic plasma level of PA tients (30 %) both slow and rapid acetylators ed the SLE-like syndrome within one year sma levels were similar in both slow and rapid tors and there was no difference in total dose at on of therapy before development of the me Thus the acetylator phenotype is prob- no or minor predictive importance when PA is guided by plasma monitoring On the hand the antinuclear antibodies appeared antly more rapidly in patients developing the me and could possibly be used as an indicator risk The results support the hypothesis that mary amino group structure of PA may be of ance in the induction of the SLE like me

rds ant nuclear ant bod es acetylator phenotype ced N acetylproca nam de procainam de lupus erythematosus

led Scand 206 245 1979

drugs have been reported to induce a lupus erythematosus (SLE) l ke syndrome g term therapy but hydralazine and pro (PA) have been implicated most fre 4 14 19 25) Both drugs have also been be polymorphically acetylated in man azid (INH) and some sulfonamides (8 9 29) and the syndrome seems to occur quently in slow than rapid acetylators (14)

A primary amino group is common to most of the drugs causing the syndrome and has been suggested as the responsible factor (7 22) Campbell et al (5) also found a correlation between acetylator phenotype and PA plasma levels for a given daily dose of PA slow acetylators had a higher mean PA plasma level than rapid acetylators However if the therapy is guided by plasma monitoring rapid and slow acetylators will probably reach the same PA plasma level and the acetylator phenotype would be of minor importance for the risk of inducing the SLE like syndrome

Earlier studies on the frequency of the SLE l ke syndrome during PA therapy have focused on the importance of the dose and acetylator phenotype The purpose of this study was to evaluate the importance of the plasma levels of unchanged PA and the metabolite N acetylprocainamide (NAPA) for the development of the syndrome

PATIENTS AND METHODS

Long term therapy with PA was initiated in 40 patients with ventricular arrhythmias motivating treatment Some clinical characteristics of the patients are given in Table I The majority had a previous history of coronary artery disease and were treated concomitantly with other drugs not known to induce the SLE l ke syndrome All patients gave their informed consent to participate in the study

Laboratory checks

Prior to the start of therapy and every second month thereafter the following parameters were checked ESR

Abbreviations SLE systemic lupus erythematosus PA procainamide INH isoniazid NAPA N acetylprocainamide ANA=antinuclear antibodies FITC fluorescein isothiocyanate DNA deoxyribonucleic acid $T_{\frac{1}{2}}$ plasma half life

Table I *Clinical characteristics of the initial 40 patients*

Age (y)	
Mean	62
Range	28–82
Females	12
Males	28
Diagnosis	
Coronary heart disease	26
Others	14
Concomitant therapy	
Digitalis	18
Diuretics	17
β adrenergic blocking drugs	22
Others	15
None	6

Hb antinuclear antibodies (ANA) serum electrophoresis The concentrations of PA and NAPA at both minimum and expected maximum plasma level were determined and the dose was adjusted in order to attain a PA plasma level within the proposed "therapeutic" range of 4–8 μg/ml (17) in all patients At every check-up the patients underwent a thorough clinical examination and were questioned about SLE symptoms The plan was to follow all patients for 12 months or until symptomatic adverse reactions arose *Thus PA therapy was not discontinued due to a raised ANA titer alone*

Criteria of the SLE-like syndrome

The following criteria were required for the diagnosis of PA-induced SLE like syndrome A significantly raised ANA titer with at least one of the following symptoms or signs arthralgia, arthritis myalgia pericarditis pleuritis pulmonic infiltration fever These symptoms and signs had also to diminish or disappear after withdrawal of PA therapy

ANA determination

Unfixed 5 μ cryostat sections of mouse kidney and liver were used as substrate to detect [illegible] against tissue constituents by indirect fluorescence technique (6) The sera [illegible] dilution of 1 25 for antibodies of the IgG class [illegible] the appropriate fluorescein isothiocyanate [illegible]gated antiserum (Wellcome used at [illegible] Fluorescence titre was established with [illegible] (1 25 1 100 1 400 etc) until an endpoint [illegible] Sera with ANA were tested for antibodies [illegible]oxyribonucleic acid (DNA) using the immunofl[illegible] test with the kinetoplast of Crithidia luciliae [illegible]strate (the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service) Titers of [illegible] either IgG or IgM were regarded as [illegible] creased

Determination of acetylator phenotype

The acetylator phenotype of each patient was [illegible] either by the INH test (37 patients) or by the [illegible]pyridine test (3 patients)

The INH test was performed by g[illegible] tient a single oral dose approximately 10 mg/k[illegible] (Tibinide®) Food intake was not [illegible] hours later Venous blood samples were [illegible] heparinized tubes before and 3 5 7 and 9 hours [illegible] INH dose The plasma was frozen until analysed [illegible]ing to the method described by Maher et al [illegible] plasma half-life ($T^1/_2$) and the overall elimination constant (k) were calculated from the regression [illegible] resenting the logarithmic decay of the concentration [illegible] time Patients with $T^1/_2$ longer than 2.1 hours were [illegible]sified as slow acetylators according to Hamp[illegible] (12)

The sulphapyridine test was performed in the [illegible] way The fasting patient was given 500 mg [illegible] (Septipulmon®) and food intake was not allowed [illegible] hours later according to Schroder and Evans [illegible] specimens collected between the 7th and 8th hour [illegible]

[illegible]II *Other reasons than SLE manifestations for discontinuing PA therapy in 12 patients*
[illegible]low acetylator R = rapid acetylator w = weeks m = months

Sex	Acetylator phenotype	Reason for withdrawing PA	Time of withdrawal of PA	ANA titer at withdrawal
♂	S	Urticaria	3 w	Neg.
♂	R	Urticaria	3 w	Neg
♀	S	Urticaria	3 m	1/100
♂	R	Hypotension + vertigo	2 w	Data missing
♀	R	Suspected asthma bronchiale	2 m	Neg.
♂	S	Voluntarily no side-effects	2 m	Neg.
♂	S	Voluntarily no side-effects	9 m	Neg.
♀	S	Voluntarily no side-effects	2 m	1/200
♂	S	Voluntarily no side-effects	5 m	1/400
♂	S	Death from left heart failure	5 m	Neg
♂	S	By mistake because of raised ANA titer	4 m	1/400
♂	S	Therapeutic failure with left heart failure and aggravated arrhythmias	8 m	1/100

II *Characteristics of 28 patints with (group ... without (group B) SLE manifestations*

	Group A (n=9)	Group B (n=19)
r		
	59	63
	47–70	28–75
	4	5
	5	14
...tor phenotype		
	7	17
	2	2
...d renal function		
...atinine >1 3 mg/100		
115 μmol/l)	1	6
...s		
...tary heart disease	7	11
s	2	8
...mitant therapy		
...ils	5	10
...tics	3	9
...energic blocking drugs	4	6
	1	4
PA dose (g)		
	646	1 156
e	135–1 620	540–1 620
PA		
...d mean±S D)		
...mum	4 6±1 8	4 0±1 4
...mum	6 7±2 2[a]	5 9±1 9
s NAPA		
...l mean±S D)		
mum	3 4±1 3[a]	4 9±3 5
...mum	3 4±1 7	5 4±3 0[d]

[a] n=6 n=4 [d] n 18

...ere analysed according to the method of Hansson ...ndberg (13)

...inat on of plasma concentration of PA and NAPA

...samples for determination of plasma levels of the ...ere centrifuged and stored frozen until analysed ...sample was analysed simultaneously for PA and by a sensitive liquid chromatography method ac... g to Graffner et al (11)

RESULTS

...y three patients were classified as slow and 7 ...id acetylators In 12 patients the therapy was ...ntinued for reasons other than development ...e SLE like syndrome (Table II) The im... ...logic status of these patients at the time of ...rawal of PA is also shown Characteristics of ...maining 28 patients 4 of whom were rapid and 24 slow acetylators are given in Table III Nineteen continued the therapy without side effects (group B)

SLE like syndrome

Nine of the 28 patients 2 rapid and 7 slow acetylators developed clinical manifestations of the SLE like syndrome (group A) The signs and symptoms indicating the syndrome are given in Table IV The earliest and most common symptom was migratory and symmetrical arthralgia The ESR was higher than the pretreatment value in only 2 patients No systematic abnormalities in the serum electrophoresis pattern and no other haematological or renal disturbances were recorded

Fig 1 shows the development of the SLE like syndrome with time It occurred less than 4 months after initiation of the PA treatment in 5 of the 9 patients one patient—a rapid acetylator—presenting typical manifestations within only 1 / months After discontinuation of the PA therapy the signs of the syndrome disappeared in all patients In most of them the symptoms improved rapidly but one patient required steroid therapy for 2 months The ANA titers returned slowly to normal and were 1/100 or less in 6 of the 7 patients who could be followed for 10 months

ANA titer

Fig 2 shows the time needed for the development of a significantly raised ANA titer (either IgG or IgM ≥1/100) after initiation of the PA therapy The ANA titer increased significantly earlier in group A than in group B ($p<0.01$ at 2 months $p<0.05$ at 4 and 8 months Fisher s exact probability test)

ANA titers at the onset of SLE manifestations in group A patients and after 12 months of PA therapy in group B patients are given in Fig 3 Patients with the SLE like syndrome had higher titers (≥1/400) than patients without In 12 of the 19 patients in

Table IV *Dominant clinical manifestations in 9 patients developing the SLE like syndrome*

	No of pats
Arthralgia	8
Arthritis	2
Pleuritis	2
Pulmonary infiltration	1
Pericarditis	1

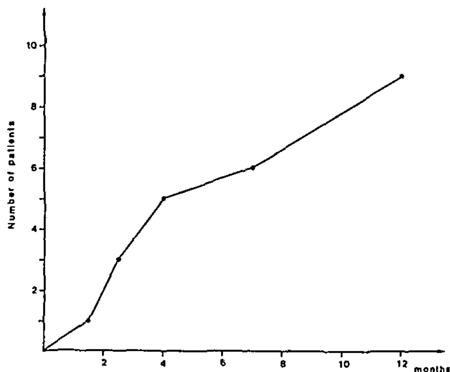


Fig 1 Time to dev of clinical manifesta patients with PA a SLE like syndrome

group B the ANA titer was significantly raised Consequently 7 patients (25%) could be treated with PA for one year or longer without any significant influence on the ANA titer

Sera from all 9 patients in group A and from the 8 in group B who developed the highest ANA titers were examined for DNA antibodies All se negative

Plasma levels of PA and NAPA

The total intake of PA and the plasma levels and NAPA are given in Table III The mea

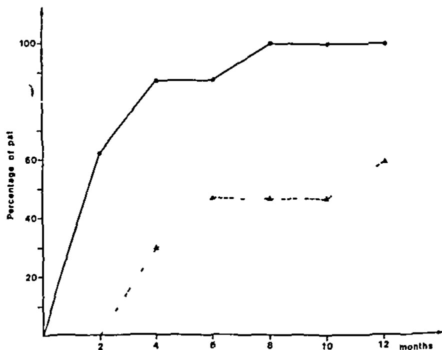


Fig 2 Time to devel of a significantly rai titer (≥1/100) in 8 gr patients (—) and 17 patients ( ) Some missing for 1 patient A and 2 patients in g

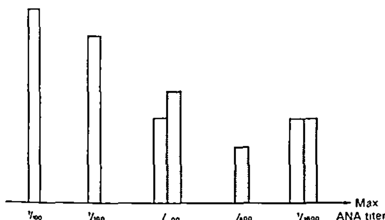


Fig 3 ANA titers at manifestation of symptoms in 9 group A patients (☐) and after one year's treatment in 19 group B patients (...)

of PA in group B was about twice that in A The plasma levels of PA were somewhat and those of NAPA lower in patients in A than in group B though the differences are tistically significant In both groups the mean concentration of PA was within the pro- therapeutic range (17) Table V shows plas- vels of PA and NAPA in rapid and slow itors PA plasma levels were the same in and slow acetylators while NAPA plasma were somewhat higher in the rapid acety This could be expected as NAPA is an ited metabolite of PA

DISCUSSION

study 9 (30%) out of 28 patients developed E like syndrome during one year on PA ent This is in good accordance with the fre found in other similar studies (3 14 19) other hand the finding by Henningsen et al at slow acetylators are more prone to develop ndrome than rapid acetylators seems less in our study Admittedly the study popula small but the rapid acetylator phenotype is tible with the development of this side effect The therapy was guided by PA plasma ing in all our patients The standard dosage Henningsen et al was much lower (1-2 an ours (mean 3 2 g/day) Consequently plasma concentrations were probably higher in our patients in most cases they reached the proposed therapeutic plasma range (17) Also with an individually tailored dosage the PA plasma concentration reaches the same level in slow and rapid acetylators Therefore if the free amino group of the PA molecule is responsible for the SLE like syndrome it is logical that the frequency of the syndrome is the same in patients of slow and rapid acetylator phenotype

Healthy subjects are reported to break down evenly into slow and rapid acetylators (15 29) The pronounced predominance of slow acetylators in the present series is difficult to explain However the same uneven distribution of phenotypes has been reported for other groups of patients with various diseases such as spontaneous SLE (20 28) tuberculosis (12) acute myocardial infarction (16) and renal diseases (24) It is conceivable that the

Table V *Steady state plasma levels of PA and NAPA (mean and range) in slow and rapid acetylators*

	Slow acetylators			Rapid acetylators		
	Mean	Range	*n*	Mean	Range	*n*
PA (μg/ml)						
Max	6 0	2 6–10 0	22	6 2	4 0–7 5	3
Min	4 1	1 6–6 9	24	4 7	2 9–5 7	3
NAPA (μg/ml)						
Max	4 9	1 9–12 5	20	6 6	5 9–7 2	2
Min	4 4	1 2 13 5	23	6 1	5 8–6 4	2

slow acetylator phenotype reflects a genetic pre disposition for a number of diseases

ANA titers rose significantly more rapidly and reached higher levels in group A than in group B Seven of the 28 patients could be treated with PA for one year without developing a significant posi tive ANA titer In comparison Kosowsky et al (19) and Henningsen et al (14) found negative ANA titers in 0 and 17% respectively after one year of PA therapy

Despite highly positive ANA titers the sera from patients with a PA induced SLE like syndrome did not contain antibodies to native DNA This finding is in accordance with those of Blomgren et al (3) and Koffler et al (18) The presence of antibodies to native DNA and consumption of complement are considered to be the best indicators of activity in SLE Neither of them have been demonstrated in PA induced SLE but are usually seen in spontane ous SLE (3) This difference may perhaps explain the milder nature of the drug induced SLE Renal changes have however been described in a few patients with PA induced SLE in whom PA therapy could not be discontinued (21 31) The milder nature of the drug induced SLE is there fore possibly explained by the prompt withdrawal of the responsible agent

According to Kosowsky et al (19) SLE like manifestations are rarely seen during the first 3 months of PA therapy However it is obvious from our data that with a higher dosage clinical symp toms of SLE can develop earlier Thus 3 of the 9 patients with SLE manifestations presented with fulminant symptoms after only 1 5–2 5 months of

In contrast to earlier reports (14 32) we found no onship between either the duration of PA therapy or the total PA dose and the development of ANA or the SLE like syndrome Thus the mean duration of PA therapy before development of the syndrome was 6 8 months in rapid acetylators against 6 3 months in slow acetylators A probable reason for these findings is that we adjusted the PA dosage in all patients in order to reach the proposed therapeutic plasma level In agreement with Campbell et al (5) we then found that the mean daily dose of PA was higher in rapid (3 6 g) than in slow acetylators (3 2 g)

In conclusion during one year of PA therapy an SLE like syndrome develops in about 30% of pa tients On the other hand the ANA titer was not even significantly raised in 25% The synd almost always reversible after discor PA therapy The use of the drug is justified in patients at high risk for lethal mias until safer antiarrhythmic drugs becom able Subjective symptoms and a rapid a nounced rise in the ANA titer are the earlie ing signs On the other hand a phenoty seems to be of little value in predicting when the therapy is guided by plasma mea resulting in the same PA plasma level in bo and rapid acetylators

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[E]ffect of Physical Training on Different Categories of Patients with Intermittent Claudication

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[ABSTR]ACT The effect of supervised training was [studied] in 68 patients with intermittent claudication [Maxima]l walking distance was measured on a [treadm]ill Eight of the patients had resting pain in the [legs whe]n recumbent (group A), 25 had an initial [walking] distance of less than 500 m (group B) 11 had [an initi]al walking distance of 500–1 000 m (group C) [and 24 had] coronary insufficiency (group D) The study [shows t]hat training should be undertaken for at least [six m]onths In some patients with resting pain [trainin]g led to relief of pain and surgical treatment [was no]t necessary Almost all patients without signs [of coro]nary insufficiency increased their walking dis[tance] compared to only 14 of the 24 patients with [corona]ry insufficiency Walking distance increased [signific]antly in groups B and C and no significant [differe]nce was found between patients with proximal [and dist]al arterial stenosis

[Key w]ords intermittent claudication physical therapy

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[Sever]al studies have shown the beneficial effect of [physic]al training in patients with intermittent [claudi]cation (4 12 14 22) Improved peripheral [extrac]tion of oxygen (22) improved glycolytic and [oxida]tive metabolic capacity (8) and improved [walki]ng technique (19) have been suggested as [reaso]ns for the improvement with training An in[crease i]n the collateral inflow capacity after training [has bee]n demonstrated in animal experiments (16) [and in c]linical studies (5) Skinner and Strandness (20) [recentl]y found an increased blood pressure (BP) [in the] ankle at rest after training and also a less [marked] reduction in ankle pressure after work [Thes]e changes were considered to result from an [incre]ased collateral circulation However Dahllof [et al f]ound no changes in BP at rest in the calf after [train]ing Some authors have considered reconstruc[tive] vascular surgery to be the treatment of choice [in re]sting pain (17) and resting pain has been regarded as an absolute indication for reconstructive surgery (6) It is well known that a high percentage of patients with intermittent claudi[ca]tion have coronary insufficiency (9) We have [not] seen any study on the effect of physical training [i]n this group of patients

Some studies have shown that the more proximal the arterial stenosis the less the effect of training (18) This finding does not accord with our experience Therefore we have undertaken a study to find out first if training has any effect on patients with resting pain second if there is a difference in the effect of training between patients with and without coronary insufficiency and third if there is a difference between patients with proximal or di[st]al arterial stenosis

METHODS AND PATIENTS

Examination

Each patient was examined by measuring the BP in the thigh calf ankle and toe with occlusion-cuffs and strain gauges Also the pulses in the femoral and popliteal arteries were evaluated with the Doppler shift technique The BPs in the legs were assessed relative to the pressure in the right arm but the pressure in the left arm was used if it was at least 10 mmHg higher than in the right arm The patients were tested before the start of training and after 1½ and 3 months of training Some patients continued training for a further 3 months and were then tested again The tests included measurement of maximal walking distance on a treadmill with a subjective evaluation of leg pain The patients started with a load of 30 W which was then increased by 30 W every 6th minute The speed of the treadmill was 1 m/s The patients walked until either the pain in the leg was no longer bearable angina pectoris occurred or general fatigue or dyspnea intervened The test was also interrupted if the systolic BP exceeded 270 mmHg ECG was recorded continuously during the test

The leg pain was rated according to a 15 grade scale modified from Borg (2) as follows 1–2 (none)—3–4 (very light)—5–6 (fairly light)—7–8 (somewhat severe)—9–10 (severe)—11–12 (very severe)—13–14 (very very severe)—15 To assess the effect of training on leg pain we

Table I *Patients with intermittent claudication who completed supervised training in 1974 76*

	N	Average age (y)	BP relative to that in the arm (mmHg)		Duration of intermittent claudication (mo)	
			Thigh	Toe	Median	Range
Group A	8	65	−24	−95	12	3–120
Group B	25	65	−35	−101	24	2–144
Group C	11	62	−29	−87	18	6–84
Group D	24	65	−32	−101	24	2–156

compared the rating of leg pain after the same distance in each of the three tests (pretraining after 1½ and 3 months) The distance chosen for each patient was the individual pretraining maximum walking distance

Patients

Seventy eight patients with a walking distance less than 1 000 m on the treadmill but without gangrene started supervised training between March 1974 and Dec 1976 Two patients discontinued training because of cox arthrosis and knee joint disease respectively Three patients were admitted to hospital during the training period because of myocardial infarction cerebral vascular disease and gastrointestinal disease respectively Two patients had to stop because of cardiomegaly and uncontrolled atrial fibrillation respectively Two patients stopped training of their own accord One patient was admitted to vascular surgery after 1 month of training The remaining 68 patients (age range 49–86 years) of whom 48 (70%) were men had had intermittent claudication for 2–156 months (Table I)

The patients were divided into four groups *Group A* 8 patients with resting pain in the leg when recumbent None of them had diabetes mellitus All had been wakened on several occasions by pain in the leg relieved when lowering the leg This pain was easily differentiated from cramp and the restless legs syndrome the latter experienced by 14 of the other patients *Group B* 25 patients who had an initial walking distance of less than *Group C* 11 patients who had an initial walking of 500–1 000 m *Group D* 24 patients with signs of insufficiency in the exercise ECG and/or a of angina pectoris There were no differences in ge age or segmental BPs between these four groups able I) Thirteen of the 36 patients in groups B and C had proximal arterial stenosis which was defined as a BP in the thigh at least 25 mmHg lower than in the arm (13) and loss of the diastolic component in the pulsations in the femoral artery evaluated with the Doppler shift technique (21)

Training

The patients trained in groups in the Department of Clinical Physiology for 30 min twice a week for three months under the guidance of a physiotherapist Eight of the patients with coronary insufficiency continued their training for another 2–3 months Before starting the training we informed the patients about the disease and the available means of treatment Also we went through a programme for training at home and impressed portance of daily walks in addition to the formal programme

The aim of the training was to increase the distance by improving peripheral circulation endurance and strength patient fitness joint walking technique co-ordination and balance The training consisted of simple movements of feet and legs until almost maximal pain occurred The most effective training is achieved in the standing position e g limbering up jumping dancing and rope skipping After each training session most of the patients also exercised on bicycles The training was adapted to the general condition of the patient For example those with coronary insufficiency started by warming up sitting and then continued alternately standing and sitting To get the peripheral effect of training in these patients without inducing angina pectoris the exercises were also performed with each leg separately

Statistics

Student s *t* test for paired and unpaired observations used for statistical calculations

RESULTS

Group A—resting pain

After three months of training six of the eight patients in this group no longer had resting pain of these six had had resting pain 1–3 times per night for two weeks to one year and a history of claudication for less than two years The sixth patient had resting pain up to three times per night for two weeks and claudication for only three months The two patients who did not improve had more frequent attacks of resting pain (> 3 times per night) for at least two months One had had claudication for three years the other for ten years

The six patients who improved more than doubled their walking distance after three months training ($p<0.01$) while the other two reached a slight increase in their walking distance

hanges n walk ng d stance and leg pa n in pat ent gro ps B C and D

	Pre train ng	Posttrain ng (mo)	
		1½	3
= 5)			
alking d stance (m)	261	47?	583
walking d stance (m)		+?11 *	+111 *
(degree)			
al walk ng d stance	12 7	10 5 *	11 3
al pretrain ng walk ng d stance 61 m)	12 7	8 7***	6 4 *
=11)			
walk ng d s ance (m)	697	740	897
walking d s ance (m)		+4?	+158 *
(degree)			
nal walking d stance	12 0	10 6	10 9
nal pretrain ng walk ng d stance 697 m)	1? 0	10 1	10 7
=?4)			
walking d stance (m)	470	598	597
walking d tance (m)		+1?8	)
maximal walking d stance (degree)	1? 0	10 5	9 5**

$p<0.01$ $p<0.001$

e

at ents who improved had an average ankle of 65 mmHg (range 45–100) the other two id 55 mmHg respectively One of these later underwent reconstruct ve vascular

walk ng d stance less tl an 500 m
I)

as a s gnif cant ncrease in walking distance months of train ng ($p<0.001$) and a further after three months ($p<0.01$) when the walking d stance was more than doubled e pat ents rat ng of the leg pain at the pre max mum walk ng d stance was significant at the 1½ month (8 7) and 3 month tests an at the pretrain ng test (12 7) ($p<0.001$) at ents except two had increased the r walk a ce at the three month test One of the two impro ement cont nued tra ning for another months and ach eved a clear ncrease at a test med thereafter

C—walk ng d stance 500–1 000 m
I))

alk ng d stance d d not ncrease s gnificantly fter three months of train ng ($p<0.01$) Also b ective assessment of leg pa n at the max imum pretra n ng walking d stance showed no im provement at e ther the 1½ month (10 1) or 3 month test (10 7) compared with the pretrain ng test (1? 0

E ght of the 11 patients increased the r walking d stance after three months of training One of the three pat ents who d d not improve had cox arthrosis and one ncreased his walk ng d stance at a test performed after a further three months

Gro p D—coronary inst ff c ency
(Tables II and III)

The pat ents in th s group increased the r walk ng d stance s gn f cantly after 1½ months of train ng ($p<0.01$) but there was no further sign f cant in crease after that After the full three months of train ng 14 patients increased the r walking d s tance wh le 10 d d not There were no d fferences n the durat on of claud cation or in segmental BPs between those who improved and those who d d not In the pat ents who improved the subjective rating of leg pa n at the maximal pretraining walking d stance (mean 450 m) was s gn ficantly lower after three months of tra n ng (7 8) than at the pretra n ng test (11 9) Those who d d not improve showed no s gn f cant d fference in the r ratings (11 1 compared to 12 2) At the three month test there were no s gnificant d fferences in the leg pa n ratings inci

Table III *Patients with ECG changes indicating coronary insufficiency during the pretraining test and/or a history of angina pectoris (group D n=24)*

	Before training	After 3 months training
Patients who improved (n=14)		
Maximal walking distance (m)	450	736
Leg pain		
At maximal pretraining walking distance (mean 450 m)	11 9	7 8
At maximal walking distance	11 9	9 6
Patients who did not improve (n=10)		
Maximal walking distance (m)	500	406
Leg pain (degree) at maximal walking distance (mean 406 m)	12 2	11 1

*$p<0.05$ $p<0.01$

dence of angina pectoris heart rate or frequency of respiration at the end of the maximal walking test between those who improved and those who did not Two of the patients who did not improve and three of those who did were on treatment with β receptor blocking drugs

Three of the patients who did not increase their walking distance after three months of training continued training for another three months After this extra period one showed an appreciable and two a moderate increase in their walking distances

able IV *Patients with proximal and distal arterial osis in groups B and C (n=36)*

	Before training	After 3 months training
Proximal arterial stenosis (n=13)		
Maximal walking distance (m)	347	687
Increase in walking distance (m)		+340 *
Leg pain (degree) at maximal pretraining walking distance (mean 347 m)	12 5	6 4 *
Distal arterial stenosis (n=23)		
Maximal walking distance (m)	440	666
Increase in walking distance (m)		+226***
Leg pain (degree) at maximal pretraining walking distance (mean 440 m)	12 6	8 7*

***$p<0.001$

Proximal vs distal arterial stenosis (Table IV)

Of the 36 patients in groups B and C 13 had mal arterial stenosis They had a significa BP in the thigh the average differenc thigh and arm being −54 mmHg against −n in the patients with distal arterial steno were no significant difference in ankle pr

Walking distances increased signific three months of training in those with p as well as in those with distal arteri ($p<0.001$) and we found no difference in t of training All but one patient among th proximal arterial stenosis increased their distance

DISCUSSION

Length of the training period

Earlier studies have shown that patients termittent claudication increased their wal tance after 3–4 months of training (4 1 Our study likewise showed an increase distance after three months of training i the patients with no signs of coronary ins In fact in group B there was already a s increase in walking distance after 11 training Some patients however needed months of training Our results support allowing patients with intermittent claudic train for at least three months before an are made concerning vascular surgery

Resting pain

Resting pain has been considered to be a indication for vascular surgery (6) wh have attempted to treat it with prostagl sions (3) In previous articles treatment hypertension and lumbal sympathectomy discussed *We found that patients with* resting pain (1–3 times per week) for a r short time (less than a year) and not more years of claudication obtained a good res training with elimination of the pain and than doubled walking distance The patients did not have the restless legs syndrome thrombotic conditions and there were n other non ischemic causes of pain Th pain of low frequency does not seem to cate a trial of training for three months

ns ffc ency

t ents w th claud cat on have s gns and/or s of coronary insuff ciency Among our 35% had coronary insuff ciency which is frequency as others have found (9) In three other pat ents had had a myocard al

74 pat ents with coronary insufficiency 14 l the r walk ng distance after three months g wh le 10 d d not Among the 10 pat ents not improve two had ang na pectoris at the ng test At the test after three months of another three pat ents had ang na pectoris uld expla n the lack of an effect of train ng W th our non nvasive methods we d d not o her d fference between the two groups uld expla n the lack of an effect of train ng ther 7 pat ents In an analysis of a large claud cat on pat ents who had undergone ed tra n ng t was found that overwe ght sion and coronary heart disease un ly influenced the change in walking d s l) Impa red function of the left ventricle one explanatory variable Hellerste n (7) n a group of pat ents with angina pectoris w thout myocardial infarction that fa ling to train ng ind cated not only more severe y artery d sease but also more severe l on of the left ventricle than response to

of the pat ents w th no improvement con rain ng for another three months and had an d walk ng distance at a test follow ng th s period of train ng Thus it is poss ble that w h coronary insuffic ency need a longer of tra n ng Dur ng the walk ng tests these walked w th a load on the treadm ll and it is that the result would have been d fferent if d walked on the flat

l s d stal arter al stenos s

w th prox mal stenosis have a h gher con on of lactate n blood from the femoral ve n than pat ents w th distal stenos s (14) y because of arterial insuff c ency in large muscle groups It has been shown that the rox mal the stenosis the less the effect of (18) We d d not f nd any s gnif cant d ffer the effect of tra n ng between patients w th and those w th d stal arter al stenos s both show ing a significant increase in walk n d tance after three months of tra n ng However n of the pat ents with prox mal stenosis had low BP in the th gh The average th gh pressu 101 mmHg (range 70–185) and the a erage d ence between th gh and arm pressure 5 mm (range −25 to 100) One would not expec t ents with a greater d fference between th gh and arm pressure to sho v such a good result from tra n ng

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Prognostic Significance of Lymphopenia in Sarcoidosis

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ACT During 1959–67, sarcoidosis was diag n a series of 140 patients All were followed 22 developed chronic sarcoidosis In 134 (20 with chronic course) the initial granulo onocyte and lymphocyte counts were known erences in granulocyte values were seen be lifferent groups of sarcoidosis patients Pa ith erythema nodosum had significantly in monocyte levels Lymphopenia below 1 000/ seen in only 7 5% of the patients Lympho ants below 1 500/μl were a common finding lly in patients developing chronic sarcoidosis antly decreased lymphocyte values were also patients older than 40 years at the time of as, in patients negative to 10 TU of PPD and e with a disease requiring treatment with teroids A correlation was found between lymphopenia and less favourable prognosis f the patients having a very good prognosis s with initial lymphopenia must be carefully d up The initial presence of erythema m does not always guarantee a good prognosis

ds sarcoidosis lymphopenia prognosis
ed Scand 206 259 1979

ognosis of sarcoidosis varies It used to be red poor because only the lesions typical of c disease were recognized Today we hat the prognosis is usually good However atients develop a chronic disease which may lmonary fibrosis with respiratory insuffi nephrocalcinosis with renal insufficiency ions and bone cysts These patients benefit long term treatment with corticosteroids eve subjective symptoms (11)

indications for corticosteroid therapy in sar is are usually clear Patients with non fibrotic nary infiltrations present a special problem lesions may disappear spontaneously but mes remain stable or deteriorate Prospective controlled studies have indicated that it is un necessary to treat every patient (18) However there is no clinical sign which indicates that a pa tient will definitely develop a chronic disease have a poor prognosis and perhaps continuously require corticosteroids

During the years 1959–67 a series of sarcoidosis patients was examined clinically (15) They have been followed up for more than 10 years We have now analysed the initial granulocyte monocyte and lymphocyte counts in the patients who subsequent ly developed a chronic disease and compared these data with corresponding values for other groups of sarcoidosis patients and healthy controls

PATIENTS AND METHODS

The investigation was carried out on 140 sarcoidosis pa tients diagnosed in 1959–67 The clinical picture and diag nostic criteria have been reported elsewhere (15) Dif ferential leukocyte count was made initially in 134 of the patients None of the patients was receiving corticosteroids for other diseases at the time of the diagnosis of sar coidosis Of the 6 patients whose initial differential count was unknown 2 developed a chronic disease

The follow up examination disclosed that 22 patients (15 7%) developed chronic sarcoidosis with pulmonary fibrosis and moderate to severe functional impairment Four patients with a chronic disease have died three of uraemia and one of respiratory failure Continuous activi ty of the disease has been a typical sign of the chronic condition presenting as a fluctuating chest X ray finding variation in lymph node size development of splenomega ly and bone cysts and often as new skin lesions

Of the 22 patients with chronic sarcoidosis 14 (64%) were females In the non-chronic group 69% were fe males (Table I) Some other clinical signs are also listed in Table I The age at diagnosis was significantly higher in the patients developing chronic disease than in those with a limited non chronic disorder Of the chronic patients 68% were initially negative to 10 TU of PPD against only 41% in the non-chronic group This difference is also significant The presence of erythema nodosum positive skin reaction to 1 TU hypercalcaemia or hypercalciuria

Table I *Initial data on 140 sarcoidosis patients diagnosed during 1959–67 and grouped accord results of follow up examinations more than 10 years later*

	Patients who developed chronic sarcoidosis (Age at diagnosis 45 5±11 0)		Patients whose sarcoidosis was cured (Age at diagnosis 38 7±10 7)	
	N	%	*N*	%
Total	22	15 7	118	84 3
Females	14	64	81	69
Erythema nodosum	2	9	27	23
1 TU +	2	9	30	25
10 TU +	5	23	40	34
10 TU −	15	68	48	41
Chest X ray				
Stage I	8	36	69	58
Stage II	14	64	49	42
Hypercalcaemia	6/21	29	16/110	15
Hypercalciuria	6/17	35	15/89	17

Statistically significant differences exist between chronic and non-chronic patients with respect to age a ($p<0\ 01$) and 10 TU negative skin reactions ($\chi^2=5\ 67$ $p<0\ 025$)

did not influence the prognosis Neither was the initial chest X ray finding a prognostic sign

The total number of leukocytes and the numbers of granulocytes monocytes and lymphocytes at the time of diagnosis were calculated in 134 sarcoidosis patients and in 40 healthy controls of the same age and sex

RESULTS

The numbers of leukocytes granulocytes monocytes and lymphocytes are shown in Table II

The leukocyte count was normal in all groups of sarcoidosis patients No significant differences were noted in granulocyte counts betw coidosis patients and healthy controls or different groups of sarcoidosis patients

The monocytes were normal in all grou coidosis patients except for those with nodosum who had a significantly increase compared with the healthy controls ($p<0$

The greatest variations were noted in phocyte counts The lowest values we among the patients who developed chr coidosis Their mean lymphocyte value was significantly lower than that of the co

II *Leukocyte granulocyte monocyte and lymphocyte counts/µl (mean±S D) at the osis in different groups of sarcoidosis patients and healthy controls*

	N	Leukocytes	Granulocytes	Monocytes	Lym
Healthy controls	40	6 600±1 500	4 146±1 360	348±215	2 01
Female patients	91	6 500±1 600	4 066±1 301	395±248	1 879
Male patients	43	6 800±2 000	4 171±1 504	457±347	1 936
Pats below 40 y	69	6800±1 800	4 233±1 369	409±250	1 944
Pats above 40 y	65	6 300±1 800	3 947±1 347	417±313	1 764
Erythema nodosum	29	7 600±1 500	4 976±1 472	510±278	1 995
1 TU +	32	6 900±2 000	4 199±1 586	427±226	2 077
Chest X ray					
Stage I	71	6 900±1 800	4 376±1 326	386±250	1 940
Stage II	63	6 200±1 700	3 772±1 347	449±315	1 749
Pats not immediately treated	79	6 900±1 700	4 312±1 362	371±222	2 038
Pats immediately treated	55	6 100±1 800	3 780±1 309	474±343	1 590
Pats developing chronic sarcoidosis	20	6 000±1 900	3 834±1 345	465±334	1 496
Pats developing non chronic disease	114	6 700±1 700	4 180±1 342	406×272	1 913

$p<0.001$) and of the sarcoidosis patients not ping a chronic disease ($p<0.01$). Out of 20 patients 12 had an initial lymphopenia iocyte count $<1500/\mu l$) the lowest value be $/\mu l$. A lymphocyte count below $1500/\mu l$ was in only 27 patients out of 118 (23%) in the group. However the disease was spontaneously in only 4 of these 27 patients; other 23 required treatment with corticols and the signs of disease activity did not ear during the first two years. Lymphocyte below $1000/\mu l$ were seen in only 10 patients mean lymphocyte values of female and male dosis patients did not differ significantly from other or from the values of the controls. r was there any difference in lymphocyte between patients above and below 40 years at the time of diagnosis. However those over irs had a slightly lower mean lymphocyte val n the controls ($p<0.05$). Sarcoidosis patients stage II pulmonary infiltrations had initially a r mean lymphocyte value than the patients it stage I finding but the difference was not ically significant.

ents whose sarcoidosis was considered so spread or active that therapy with corticods was started immediately had a significantly r mean lymphocyte value than the controls .001) and the patients not requiring steroids .001). The later had the highest mean lymte value ($2038/\mu l$) together with those with a ve skin reaction to 1TU of PPD ($2072/\mu l$).

DISCUSSION

reviews state that leukopenia is not an unusu g in sarcoidosis (1, 13). The leukopenia was nd to be due to a reduction of lymphocytes nd (10) noted that 33% of sarcoidosis pa ad lymphocyte counts below $1000/\mu l$ and an lymphocyte value was significantly low that of healthy controls. He also found that penia was more common in patients with hout radiographic evidence of lung involve d in patients with chronic persistent dis n in those with subacute transient disease (2) found the same frequency of initial lym a among 140 patients with pulmonary stage sarcoidosis.

occurrence of lymphopenia in sarcoidosis n repeatedly verified and shown to be due to a reduction in thymus-dependent lymphocytes—T cells (5, 6, 9, 12, 14, 19, 20 and the present stu The number of B-cells is either normal, re duced (20) or slightly elevated (6, 7, 14). Estim of lymphocyte subpopulations could not be out at the time of diagnosis in our patients.

Böttger (3) has drawn attention to rising lymph cyte values in patients with spontaneously regre ing disease. Patients on corticosteroid therap have lower lymphocyte values than non treated sarcoidosis patients (14). In patients treated with corticosteroids the relapse rate after treatment has been found to be significantly higher among those with persistent lymphopenia (4).

In Finland the prognosis of sarcoidosis is usually good (15, 17) and particularly favourable when as sociated with female sex, young age, erythema nodosum and positive skin tests with 0.1–1 TU of PPD (8). The prognosis was not influenced by dif ferences in sex, presence of erythema nodosum o initial chest X ray findings in our series. Patients negative to 10 TU of PPD had a poorer prognosis than those positive to 10 TU. The lymphocyte val ues were as a rule significantly lower in patient with a poor prognosis.

A correlation exists between the prognosis sarcoidosis and delayed type hypersensitivity reac tions. In Finland, sarcoidosis patients as a group have depressed skin reactivity to PPD, but indi vidual patients may not show any reduction (15). Most patients with a depressed reactivity to PPD at the time of diagnosis regain their normal skin sen sitivity to PPD when sarcoidosis is cured—sponta neously or after treatment with corticosteroids (16). Patients with a less favourable prognosis usually remain tuberculin negative. The delayed type hy persensitivity reactions are controlled by the T cells. It is therefore understandable that a reduction in lymphocytes caused by a depletion of T-cells is correlated with the prognosis of the disease (21).

This investigation clearly indicates the relation ship between lymphopenia and the prognosis of sarcoidosis. The initial lymphopenia in this popula tion (lymphocytes $<1500/\mu l$) seems to be of greater prognostic significance than previously believed. Initial lymphopenia was a common finding among the patients who developed a chronic disease but very rare among those who had a disease with good prognosis. This obvious difference may be partly influenced by the composition of the series in our country, where initial lymphopenia below $1000/\mu l$

is a rare finding in sarcoidosis patients Lymphopenia of this degree was seen in only 10 (7 5%) of our patients compared to one third of patients in other series (2 10)

Although a small proportion of the sarcoidosis patients with initial lymphopenia have a good prognosis the finding of lymphocyte reduction usually heralds a long standing and chronic disease with a poor prognosis The finding of initial lymphopenia *indicates a very careful follow up On the other* hand those with initially normal or high lymphocyte counts and usually—as a consequence of this—positive skin reactions to at least 10 TU of PPD have a good prognosis and can be followed up without therapy

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Glibenclamide and Glipizide in Maturity Onset Diabetes

A Double Blind Cross over Study

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T The effects of glibenclamide and
i the concentrations of S-glucose S-insulin
s and on the 24-hour urinary glucose ex
re studied in 37 patients with maturity
tes A double blind cross-over, double-
chnique was used The fasting S-insulin
on was higher during glibenclamide
hile the increase in insulin concentration
postprandially was stronger during
herapy supporting the concept that
ide has a more prolonged and glipizide a
acting effect on insulin secretion The S-
centration was lower in the fasting state as
hour postprandially during glibenclamide
ich together with a lower 24-hour urinary
retion indicates that glibenclamide has a
lood glucose lowering effect Although
significant, the differences were marginal
nical point of view The lipid levels re-
changed

maturity onset diabetes double blind cross-
nclamide glipizide sulphonylureas hypo-
ulphonamides oral antidiabetic substances

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f treating maturity onset diabetes is not
lieve symptoms but also to prevent late
omplications including cardiovascular
t is generally accepted that normalization
od glucose homeostasis is essential to
ese aims A diet restricted in fat and
bohydrates and thus in energy is in com
with exercise the mainstay of diabetes
leading to desirable weight reduction in
t always overweight maturity onset dia
en diet and exercise are not capable of
g the blood glucose level a sul
a (SU) derivative is nowadays the drug
as biguanides carry a risk of lactic
3)

In the so-called second generation group of th SU glibenclamide and glipizide—both with we documented potent antidiabetic properties (10 1 and low toxicity (14 17 23)—exhibit interes pharmacokinetic and pharmacodynamic d ferences (1 5 12 19) which may affect the clinic effe with respect to the possibility of maintaining a nor mal blood glucose level both in the present and in the future i e prevention of possible secondary failure

When comparing short term effects of dru in a clinical trial several factors irrespective of the drug itself may influence the results This is e p cially true with respect to the blood glucose lowe ing effect of antidiabetic drugs as the results are t a extremely dependent on the patients adher ence to their diet and their exercise The psycho logical effect of changing the drug will conscious ly or unconsciously lead to a tightening up of the diet One can never be sure when changing SU drugs whether the better balance in the blood glu cose homeostasis depends on the change itself or which is more probable changes in other factors

In an attempt to eliminate these very important auxiliary factors the present comparative short term study between glibenclamide and glipizide was undertaken with a double blind cross-over tech nique Diabetics with hyperglycaemia despite 15 mg of one or the other of the drugs daily were se lected in order to elucidate the difference in serum glucose and serum insulin levels as well as in the excretion of glucose in urine per 24 hours

STUDY POPULATION AND METHODS

Forty patients with maturity onset diabetes—20 on gliben clamide and 20 on glipizide—were chosen according to the following criteria 1) Fasting S-glucose >7.2 mmol/l with or without glucosuria despite 15 mg of glibenclamide or glipizide in divided doses If the patient
in combination with the SU therapy this

Table I. Clinical data on the patients (mean and range)

Treatment group	n	Age (y)	Duration of diabetes (y)	Body weight (kg)	Relative body weight (%)	[illegible]
Glibenclamide (8 men 11 women)	19	66.3 (51–77)	9.1 (4–18)	72.1 (57.6–86.6)	116.7 (94.3–131.5)	[illegible]
Glipizide (14 men 4 women)	18	62.9 (53–78)	9.8 (1–16)	77.4 (63.2–101.0)	114.[illegible] (8[illegible]–130.5)	[illegible]

during the study. About 50% of the patients had this combination. 2) For a long time on a diet restricted in respect of fat and "fast" carbohydrates. The diet had been investigated, balanced and checked by a dietitian several times. 3) Good health, i.e. no clinical symptoms of diabetes. 4) No major changes in glucose homeostasis or body weight in recent months. 5) No acute infections. Normal ESR or if slightly elevated at the same level for a long time. 6) No serious diseases other than diabetes which could be expected to interfere with the study. Drugs such as diuretics and other antihypertensives were kept constant during the study. Three patients, one in the glibenclamide and two in the glipizide group, were dropped from the study owing to intercurrent diseases. The ultimate study population is presented in Table I.

The study was carried out with a double-blind cross-over double-dummy technique. The 20 patients on glibenclamide and the 20 on glipizide were randomized separately to start with either glibenclamide or glipizide. Thus one half of the patients started with each drug within two months. After 4–6 weeks they switched over to the other drug, each patient thus being his own control. As a blind study was essential, placebo tablets of one drug were given together with the active substance of the other. The dosage was 10 mg of active substance together with breakfast and 5 mg together with the evening meal (at ... 5 p.m.).

Randomizing, loading of tablet containers and coding were performed by the local chemist. Glibenclamide, glipizide and placebo tablets were supplied by Boehringer Mannheim, Mannheim, West Germany, and Carlo Erba Research Institute, Milan, Italy.

During the test period each patient was examined three times: first on entering the study and then after each blind period. They came to the laboratory on Wednesday, Thursday or Friday in the morning in the fasting state. The study was carried through during Sept.–Dec. and was ended before the Christmas holidays. The following variables were examined: body weight, fasting values of S-glucose, S-insulin, S-cholesterol, S-triglycerides, S-creatinine, B-haemoglobin and ESR, glucosuria/24 hours.

One hour after a standardized meal (two sandwiches and 3.0 ml low-fat (0.5%) milk, about 1760 kJ = 420 kcal, CH 38%), together with which the relevant SU drug was taken, a new venous blood sample was taken for determination of S-glucose and S-insulin.

Serum was separated from the blood within one hour and stored at −20°C until analyzed. S-glu[cose was de]termined after deproteinization with a glu[cose oxidase] method (Boehringer Mannheim, kit no. [illegible]) ... was measured by means of a commercia[l] radioimmunoassay (Phadebas Insulin Test, [Pharmacia,] Uppsala, Sweden (25)). Urinary glucose [was determined] with an o-toluidine method (13). S-ch[olesterol according] to a modification of the method of Fran[...] (11) and S-triglycerides according to a modifi[cation of the] method of Carlson and Wadström (4). The deg[ree of obesi]ty was expressed as relative body weight [in per]cent of "ideal weight" as obtained from a [...] table (15).

The statistical significance of differences [was tested by] Wilcoxon matched paired signed rank test [...] unless stated otherwise). The difference wa[s considered] significant for values of $p < 0.05$.

RESULTS

Mean concentrations of the investigated [variables] 4–6 weeks after treatment with glibencl[amide and] glipizide respectively are presented in [Tables II] and III. A significantly lower fasting glu[cose level] after the glibenclamide period was associ[ated with a] significantly higher fasting insulin level.

The standardized meal gave a significant [increase in] insulin level one hour postprandially [...] glipizide period associated with a [...] although not statistically significant, [...] increase in postprandial blood glucose.

The lower blood glucose level, fasting [and] postprandially, after the glibenclamide p[eriod was] associated with a significantly lower glu[cosuria dur]ing the day before the standard meal. N[o] differences were found in lipid level[s or body] weight between the two periods. In a[ccordance] with the randomization one half of the p[atients did] not change drug when they entered the dr[ug] study. In spite of this a significant (o[...]) fall in S-glucose, both fasting from 1[...] 13.5±3.2 mmol/l ($p < 0.01$) and postprand[ially ...]

II S glucose S insulin and U glucose (mean ± S D) in 37 patients 4–6 weeks after a daily d s f ··· clamide or glipizide

calculations based on individual differences n s = not significant

	S-glucose (mmol/l)			S insulin (mU/l)			U glu (mmol ··)
	Fasting	1 hour	Difference	Fasting	1 hour	Difference	
ide	12 5±3 2	18 2±3 7	5 7±1 7	12 7±7 9	26 1±18 6	13 4±12 6	128 5±1.. (range 0–45·)
	14 1±3 4	19 2±3 9	5 1±1 7	11 0±5 9	29 7±20 7	18 7±16 6	182 1±193 6 (range 0–748)
	<0 001	<0 05	n s	<0 02	<0 01	<0 001	<0 01

o 18 9±3 8 mmol/l (p<0 05) was found ie first and second visit to the clinic in nts The 24 hour urinary glucose excre ; the day before the test did not fall 174 1±108 4 and 178 7±175 6 mmol re

effects including hypoglycaemic reac ther drug were noted during the study

DISCUSSION

al trial was performed on patients with nset diabetes who had been followed by physician at the same outpatient clinic es often for a long time Standardized or dietary treatment (dietitian) me us therapy and diabetic control had been rior to the study guaranteeing as homo patient material as possible

ents had fasting hyperglycaemia and in glucosuria despite glibenclamide or the recommended maximum dosage (15 but had no clinical symptoms of diabetes

lipids and body weight (mean ± S D) in 4–6 weeks after a daily dose of 15 mg de or glipizide

alculations based on individual differences gnificant

	S-chol esterol (mmol/l)	S-tri glycerides (mmol/l)	Body weight (kg)
le	6 77±1 28	2 36±1 14	74 6±9 5
	6 80±1 24	2 39±1 06	74 4±9 6
	n s	n s	n s

such as thirst polyuria tiredness ketonuri weight loss The manifest disturbance in their gl cose homeostasis made it impossible to have a placebo period between the two active dr·· periods as proposed by the Committee on the Use of Therapeutic Agents of the American Diabete Association (9)

The duration of each period of active substance was limited to 4–6 weeks the aim being to carry out a study during the autumn term to avoid the influ ence of Christmas celebrations The influence seasonal variations and a possible deterioration glucose homeostasis with time was further reduced by performing the study with cross-over technique To avoid weekend influences on glucose ho meostasis the patients visited the clinic on Wednesday–Friday To avoid placebo effects of the drugs as well as other psychological effects such as for example an unconscious tightening up on the diet or exercise when starting a new drug the study was performed with a double blind technique The active tablets of glibenclamide and glipizide looked different but this was overcome by a double dummy procedure in which the patients were given the active substance of one drug and placebo tablets of the other All possible precautions were thus under taken to eliminate the effects of factors other than the drug on glucose insulin and lipid homeostasis

Glibenclamide (20) and glipizide (2 12 22) have been shown to be practically completely absorbed The absorption of glipizide has however been re ported to be faster with maximal serum concentra tions of the drug at around one hour (12 23) com pared with 2–5 hours for glibenclamide (5 12 21) Compared with glibenclamide the insulin secretion after glipizide given orally in combination with food starts earlier and is of shorter duration (1 7 8 16

21) Also the effect on the blood glucose concentration is faster after glipizide (1 19) The sustained *effect on insulin secretion after glibenclamide is not* merely an effect of delayed intestinal absorption as it is found also after intravenous administration of the drug (1) The prolonged effect of glibenclamide on insulin secretion might be responsible for the higher fasting insulin level as well as for the lower fasting blood glucose concentration after the glibenclamide period A normalization of the morning blood glucose level is often considered very important for glucose homeostasis during the rest of the day The faster insulin secretion after glipizide would explain the higher serum insulin level one hour after the standardized meal The higher postprandial insulin level after glipizide gave a marginally lower increase of the postprandial blood glucose concentration but could not overcome the effect of the higher fasting blood glucose level and thus left the patients with a marginally higher blood glucose level even postprandially The higher 24-hour urine glucose excretion during glipizide therapy indicates that the blood glucose concentration remains on a higher level throughout the day when compared with glibenclamide therapy

In these patients requiring a high dosage of SU glibenclamide seems to have a somewhat more potent blood glucose lowering effect in the fasting state as well as during the day The observed marginal differences found may be a matter of non equipotency even though the drugs were given in amounts generally accepted to be equipotent (24) In an individual case a residual hyperglycaemia despite 15 mg of glibenclamide or glipizide daily ... to an increase of the dose to 20–25 mg a... th drugs have a very low toxicity (14 17 ... inical experience shows however that ... gains are seldom achieved The routine ... of 10 mg with breakfast and 5 mg with evening meal may be changed to more divided dosages especially of glipizide In a patient with morning hyperglycaemia one dosage may be tried with a late evening meal

In SU treated patients with normalized glucose homeostasis the faster and shorter insulin secretion after glipizide may be of value for avoiding hyperinsulinaemia as well as hypoglycaemia between meals This might be of especial importance during weight reduction

There is no convincing evidence that the degree of secondary failure rate differs between SU drugs

The earlier onset of effect and shorter d... insulin secretion after glipizide might have ... *effect on the β-cell function On the ot...* chlorpropamide which is even longer act... glibenclamide has in one study been found ... a tendency to a lower rate of secondary ... compared with glibenclamide (6) A l... prospective study will soon be commen... out whether there is any difference in the ... secondary failure between short and lo... SU drugs

The psychological effect of changing ... demonstrated by the fact that the patients ... accordance with the randomization did no... active substance when entering the do... study had a significantly lower fasting bloo... level after the first blind period than at th... the trial These observations firmly st... comparative studies must be performed un... trolled conditions

The lipid concentrations remained u... during the study underlining the concept ... glibenclamide and glipizide are potent an... which differ only marginally

This short term comparative study ... glibenclamide and glipizide was focused ... short term effects on glucose insulin ... homeostasis The very important long-te... of diabetes therapy were not investigated ... field on long term effects on cardio... morbidity and mortality substances with ... effects on thrombocyte adhesiveness thro... aggregation and effects on the fibrinolytic ... may achieve great importance

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tabolic Effects of Glucocorticoid and Ethanol Administration in Phenformin- and Metformin-Treated Obese Diabetics

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ACT Glucocorticoid administration for 24 o phenformin treated obese diabetics in blood lactate and lactate/pyruvate (L/P) ratio r levels than those found when only one drug n In one of 10 subjects a metabolic acidosis blood lactate of 6 2 mmol developed during eous administration of the two drugs Dia eated with phenformin or metformin in equi dosages exhibited the highest blood lactate tio and β hydroxybutyrate levels during min treatment both before and during rticoid administration Ethanol administra biguanide treated diabetics resulted in identi eases in blood lactate and L/P ratio during min and metformin treatment These find e consistent with the hypothesis that phen has a stronger inhibitory effect of gluco sis than metformin This may be one reason tic acidosis is seen much more often in phen than metformin-treated patients

rds biguanides diabetes ethanol glucocorticoid

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t findings suggest that many cases of lactic s in phenformin and metformin treated ks are caused by increased drug accumula e to decreased hepatic and renal elimination 13) Although increased biguanide accumula ay be a major factor in the development of acidosis the much more frequent occurrence s condition in phenformin than metformin d patients is unexplained and suggests that the rugs may have different effects on lactate olism

patients who developed lactic acidosis dur nide therapy have suffered from complicat iseases as pneumonia or coronary occlusion In these states the glucocorticoid production is increased and since glucocorticoid administration increases the lactate concentration in blood (11) it is conceivable that the increased glucocorticoid production could contribute to the development of lactic acidosis

We investigated the metabolic effects of glucocorticoid administration in phenformin treated diabetics In order to compare the metabolic effects of metformin and phenformin we also studied the metabolic changes during glucocorticoid and ethanol administration in patients treated with these biguanides

PATIENTS AND METHODS

Fourteen obese patients aged 50–67 years with stable diabetes mellitus treated with biguanides for 1–3 years took part in three separate studies The patients showed no evidence of hepatic renal or cardiac disease They were fully informed of the aim and nature of the investigation before giving their consent to participate The patients were admitted to hospital received a diet containing 1 300 kcal daily during the study and were allowed to walk freely around in the department They had breakfast at 08 10 lunch at 12 10 and dinner at 18 10

Study I

During the first 4 days of hospitalisation 5 patients received phenformin (Dibein®) capsules of 50 mg at 08 00 12 00 and 18 00 Phenformin was not administered on the 5th day On the 4th and 5th day hydrocortisone succinate (Solu Cortef®) corresponding to 7 mg hydrocortisone was administered intravenously every hour A preliminary study showed that this dosage regimen results in approximately a doubling of plasma cortisol During the 3rd 4th and 5th day at 18 00 and 24 00 arterial blood was drawn for determination of lactate pyruvate (3) glucose (glucose oxidase method) β hydroxybutyrate (4) standard bicarbonate and pH

Study II

A cross over study was performed in 5 patients One week before and during their stay in hospital the patients received phenformin (Dibein®) or metformin (Glucophage®)

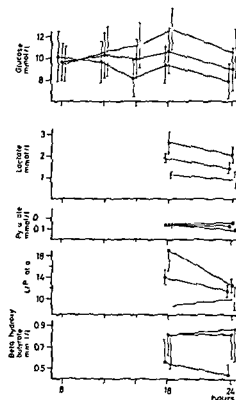


Fig 1 Metabolite concentration during three con days in 5 obese diabetics treated with phenfor phenformin+hydrocortisone succinate (O) and cortisone succinate (×)

Statistical analysis

	Glucose	Lactate	Pyruvate	L/P	β hydroxy butyrate
Phenformin ~ phenformin + steroid	N S	$p<0\ 05$	N S	$p<0\ 05$	N S
Steroid ~ phenformin + steroid	$p<0\ 05$	$p<0\ 02$	$p<0\ 02$	$p<0\ 02$	N S
Phenformin ~ steroid	N S	$p<0\ 01$	$p<0\ 01$	$p<0\ 05$	N S

00 12 00 and 18 00 daily in doses of 50 mg and 1 000 i d respectively Arterial blood was drawn at 12 00 00 24 00 and 08 00 on the first and second day of ospitalisation Hydrocortisone xanthogenate (Solvisat®) corresponding to 7 mg hydrocortisone was administered intravenously every hour during the second day blood samples being drawn as on the first day

After the first period of investigation the medication was changed to the other biguanide preparation After one week s treatment the procedure was repeated Three patients were treated with phenformin and two with metformin during the first period of investigation

Study III

Four patients were examined in a cross-over study Phenformin or metformin was administered as in study II After an overnight fast an indwelling catheter was inserted into the left femoral or brachial artery The catheter was flushed every 5th min with 5 ml isotonic saline The patients ingested 30 g ethanol in a volume of 150 ml within 1 min Arterial blood was drawn 15 and 1 min befor 60 75 90 105 120 min after ethanol ingestion

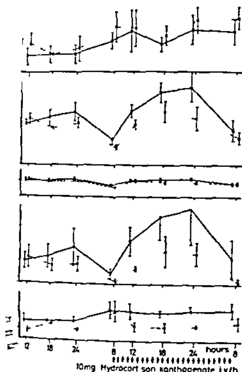
Statistics

Results are given as mean±S E M Students t paired data was used if not otherwise indicated

RESULTS

In phenformin treated obese diabetics corticoid administration resulted in mo lactate and lactate/pyruvate (L/P) ratio Aft continuation of phenformin administration gl cose concentration increased as expected lactate pyruvate and L/P ratio fell to values those found when phenformin alone was ministered (Fig 1)

Phenformin treatment resulted in signif



Blood metabolite concentrations in phenformin/metformin-treated (■) obese diabetics before and hydrocortisone xanthogenate administration

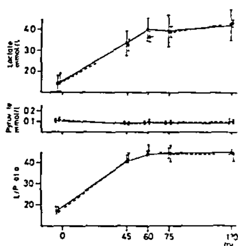


Fig 3 Blood metabolite concentrations in phenformin (□) and metformin treated (■) obese diabetics before and after ethanol administration

lactate concentrations than metformin both and during glucocorticoid administration (1) The administration of glucocorticoids significant increase in lactate concentration treatment with both biguanides ($p<0.01$ way analysis of variance) (Fig 2)

...ng simultaneous administration of gluco...d and phenformin one patient devel... metabolic acidosis (standard bicarbonate ...mol lactate 6 2 mmol/l L/P ratio 50) During ...rmin treatment the same patient exhibited a ... blood lactate of 1 2 mmol without ...us

...two biguanide preparations gave the same ...ate concentrations and glucocorticoid ad...tration did not change the pyruvate levels ...) A significantly higher L/P ratio was found ...g phenformin than during metformin adminis...n ($p<0.01$) Glucocorticoid increased the L/P ...significantly during treatment with both ...nides ($p<0.005$ three way analysis of var...) (Fig 2)

...statistically significant difference in blood glucose values was found during treatment with the two biguanide preparations However the majority of the blood glucose values in the metformin period were higher than in the phenformin period and real difference between the two periods cannot be excluded (Fig 2)

Plasma β hydroxybutyrate was significantly higher during treatment with phenformin than with metformin ($p<0.005$ three way analysis of variance) (Fig 2)

Administration of ethanol resulted in an equal increase in blood lactate and L/P ratio during treatment with phenformin and metformin (Fig 3)

DISCUSSION

The present investigation has shown that biguanide and glucocorticoid have a synergistic action on blood lactate concentration and L/P ratio Recent studies have shown an increase in blood concentrations of lactate alanine and glycerol during biguanide therapy (18) and these authors suggest that this effect of biguanide is caused by an inhibitory action on gluconeogenesis This hypothesis is supported by studies in animals (1 8 17) and humans (5 10 16)

Since glucocorticoid administration induces an increased mobilisation of gluconeogenetic precursors from muscle (12) the additive effect of the two drugs can be explained as a result of increased mobilisation and decreased utilisation of gluconeogenetic precursors

In accordance with previous investigators (18) we found increased L/P ratio during therapy with biguanides suggesting that the drugs interfere with hepatic cellular oxidation and increase the cytosolic NADH/NAD ratio Since a similar effect of gluco corticoids has been reported (19) the additive effect of biguanides and steroids on the L/P ratio is con sistent with this theory

The changes in blood lactate and L/P ratio during combined administration of biguanide and gluco-corticoid follow the same pattern although much less pronounced as in biguanide associated lactic acidosis In only one of our 10 patients the in crease in lactate was accompanied by a reduction of standard bicarbonate to values below normal However in disease states as cardiac infarction and infections often associated with lactic acidosis in biguanide treated patients the production of both glucocorticoids and catecholamines is increased Catecholamines increase blood lactate (6) and lac tic acidosis has been reported in pheochromocyto-ma (14) Therefore it seems probable that the com bined effect of increased glucocorticoid and cat echolamine levels on lactic acid metabolism con tribute to the lactic acidosis seen in biguanide treated diabetics during complicating diseases

Higher blood lactate L/P ratio and β hydroxy butyrate values were found during phenformin than metformin treatment both before and during glucocorticoid administration These findings cor respond to those reported in previous studies in diabetics not treated with glucocorticoid (9 18)

Our results rise the question whether the differ ces in blood metabolite concentrations during ent with phenformin and metformin are d by the chosen dosages Our data do not lude this possibility However in a recent study 8) a dose of metformin smaller than that used by us had the same hypoglycemic effect as our dose of phenformin Therefore our findings suggest that when the two biguanides are used in equipotent dosages phenformin causes the highest blood lactate and L/P ratio This probably reflects a stronger inhibitory effect of phenformin on hepatic cellular oxidation and gluconeogenesis The higher β hydroxybutyrate and β hydroxybutyrate/aceto-acetate ratio during phenformin than during met formin treatment found by us and other authors (18) support this hypothesis

Administration of ethanol during treatment with the two biguanides caused identical increases in blood lactate and L/P ratios Ethanol is a ... inhibitor of gluconeogenesis and these ch... *may result from a common inhibitory ef...* biguanides and ethanol on this process

That no differences were found between ethanol induced metabolic changes during ... formin and phenformin treatment may be expla... by a much stronger inhibition of gluconeogenesis by ethanol than by the biguanides

ACKNOWLEDGEMENT

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Clinical Significance of Abnormal Heterogeneity of Transferrin in Relation to Alcohol Consumption

Helena St bler Stefan Borg and Christer Allgulander

F om tl e Depa t ent f Ne lo and K r l ska Ins e Cl n al Depa n en of Alcohol and D g Researcl Karol nsk H sp l S ckl ln Sweden

ACT An abnormal microheterogeneous ent of serum transferrin with a higher ic po nt than the normal main component hed by means of isoelectric focusing and di nunof xation in 98 alcohol c patients 22 pa th h er diseases and 100 controls Its relation and prolonged ethanol intake was studied in olunteers The abnormal transferrin com was found to be a sensitive indicator of pro high alcohol ingestion and was observed in pat ents w th an admitted consumption of an 60 g ethanol/day and normalized after at da s of abst nence It occurred in 1 % of the s and in none of the cases with liver diseases current alcohol abuse There is evidence of a l s al c acid content in the abnormal transfer s m lar change has been found in a number of lycoprote ns Th s test may be a useful and e tool for the detection of chronic alcohol con on

d a cohol sm l er d seases transferrin serum soelec ric focus ng mmunof xat on serum glutamyl transfera e

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l b ochem cal abnormalit es may be found in it on w h excess ve alcohol intake and some n are often used as markers in the diagnosis ohol sm One commonly recommended ind s est mat on of the gamma glutamyl trans activ ty n serum (S GT) wh ch has been ed to be ncreased in 54–88% of chron c al cs (7 9 11 12 14 15 17) Increases n serum l pop o e ns can be observed n 40–87% of l c pa ents (6 7) and elevated serum iron a e the rule in assoc at on w th alcohol in t on (4 5 23 24) These and most other labo te ts a e however unsatisfactory because of their lack of spec f c ty For example the g mm glutamyl transferase activity is usually n e e l also in l ver diseases of non alcohol c o g n l

Recently Shaw et al (15 16) reported an r re sed quot ent between alpha am no butyr d d leucine in plasma of chronic alcohol c T te t gave positive results in 57% of the r c s and f t was comb ned with determ nation of the gam ma glutamyl transferase act vity a pos t ve d agnos was obta ned in 81% The value of the alph am no i butyr c acid/leucine quot ent can ho ever not yet be cons dered to be establ shed (10

Dur ng the exam nat on of the cerebrosp nal flu d and serum prote ns by means of analyt cal isoelec tric focusing n pat ents w th neurolog cal d seases t was observed that several pat ents with alcohol c cerebellar atax a had a qual tat ve abnormal ty of the r serum transferrin (19 22) In a subsequent report this transferrin change was found n 15 out of 16 alcohol cs and was revers ble w thin 7 14 days of alcohol abst nence The abnormal ty cons sts of a qual tat ve alterat on of the microheterogene ty of transferrin w th the appearance of a marked more pos tively charged component having an isoelec tric pH of 5 7 (?1)

The purpose of this nvestigat on was to deter mine 1) the occurrence of this transferrin abnor mality in alcohol cs in relat on to the da ly alcohol intake 2) its spec f c ty for alcoholism as compared to pat ents with d fferent l ver d seases 3) its sen s t v ty by exam nation of healthy volunteers dur ng alcohol ingest on

STUDY POPULATION

Con s

These were 100 volunteers cons dered heal hy acco d ng to h story and phys cal exam nat on In no nstance was

Table I *Clinical data and results of isoelectric focusing of serum and S GT determination in 100 co[ntrols,] 98 alcoholic patients and 22 patients with liver diseases*

	N	Age range (y)	Sex ♂	Sex ♀	% with abnormal transferrin	% with increased S-GT (>1 0 μkat/l)
Controls	100	19–65	50	50	1	-
Alcoholics	98	22–75	78	20		
Group I	26	24–75	19	7	8	8
Group II	20	34–74	20	0	25	42
Group III	20	22–63	12	8	75	47
Group IV	32	27–67	27	5	81	77
Liver diseases	22	36–72	9	13	0	84

Group I=no admitted alcohol consumption for 3 weeks group II=an admitted average of 7–20 g alcohol/day [during the] previous week group III=20–60 g alcohol/day during the previous week group IV=>60 g alcohol/day [during the] previous week None of the patients with liver diseases had any current alcohol abuse

any regular excessive alcohol consumption suspected No one was on any drug therapy apart from one female who used an oral contraceptive The age range was 19–65 years and 50 were males and 50 females (Table I)

Three of the male volunteers aged 29–34 years participated in the experiment involving ingestion of a single high ethanol dose Eight of the controls five females and three males aged 19–32 years volunteered for the experiment involving daily consumption of ethanol over a period of 7 days (see below) These experiments were approved of by the Ethical Committee of the Karolinska Institute

Alcoholic patients

Ninety eight patients treated at the Karolinska Institute Clinical Department of Alcohol and Drug Research were examined Seventy-eight were males and 20 females with in the age range 22–75 years All patients fulfilled the criteria of alcohol dependence according to WHO (28) Alcoholism was estimated to have lasted for 4–40 years The patients were divided into four groups according to the daily average of the admitted amount of alcohol con[su]med during the previous week in groups II–IV and dur[ing the] previous three weeks in group I (Table I) The [clinica]l histories revealed three patients with biopsy veri[fied c]irrhosis of the liver three with clinical and laborato[ry] signs of hepatic insufficiency two with diabetes mel[l]itus five with hypertension and five with heart disease Seven subjects had previously had alcoholic delir[ium tre]mens 16 had suffered from epileptic seizures [during ab]stinence and nine had a previous history of drug [abuse]

Patients with liver diseases without current alcohol abuse

Twenty two patients with different liver diseas[es, pro]vided by B Angelin Department of Internal M[edicine] Serafimerlasarettet Stockholm) were examined [Nine] were males and 13 females aged 36–72 years [All but] those with liver malignancy were outpatients [...] clinical condition The diagnoses were based on [clinical] and laboratory evaluation and in all cases exce[pt those] with alcoholic cirrhosis also on pathological exa[mination] of liver biopsy material (H Glaumann Depar[tment of] Pathology Huddinge Hospital Stockholm) In [no in]stance was any current alcohol abuse admitted [or sus]pected and apart from the five patients with La[ennec's] cirrhosis no one gave any history of previous [alcohol] abuse (Table II)

Table II *Diagnoses of 22 patients with liver diseases without current alcohol abuse*

	N
Laennec s cirrhosis	5
Primary biliary cirrhosis	3
Chronic active hepatitis	5
Haemochromatosis with cirrhosis	2
Fatty liver	1
Allergic hepatopathy	1
Metastases	2
Primary hepatic carcinoma	1
Hepatopathy NUD	2

METHODS

Sampling

Serum samples were taken in the morning w[ith the sub]jects fasting From the alcoholic patients in group[s II–IV] the samples were collected either during current [alcohol] abuse or at the latest on the third day after cess[ation of] drinking For isoelectric focusing the samples we[re] analyzed immediately or frozen and stored at −2[0°C for at] the most 6 months before analysis (21)

Isoelectric focusing

Analytical isoelectric focusing was carried out in [...] of polyacrylamide gel essentially according to Ve[sterberg] (26 27) as modified by Kjellin and Vesterberg [and] Stibler (18 19) The gel concentrations were T [...] C=3% Sucrose was present in 12% (w/v) and [...] 0 00005% (w/v) was used as initiator of the polymerization of the gels The pH gradient cove[red the] range 3 5–11 0 and the final Ampholine (LKB B[...]

concentration was 2% (w/v) The electrode dis 18 5 cm Each serum sample was diluted 1 10 lled water and thereafter a sample of 30 μl was a small piece of surgical lint (Robinson Ches ngland) and placed centrally on the gel surface ost 30 samples were analyzed on the same gel electrofocusing cell type F and a constant wat r supply P 101 were obtained from AB Analys allentuna Sweden The maximal voltage was nd maximal wattage 40 W The separations were after 75 min The pH measurements were per ith a surface electrode type LOT 403-30-M8 (In ch Switzerland) at +20°C (26) Staining with e Brilliant Blue R 250 (ICI Manchester Eng d destaining were carried out according to Ves 26)

xation

munofixation following isoelectric focusing was nt as described by Stibler (20) Two identical gels g the same samples were analyzed simultaneous ins of isoelectric focusing Thereafter one gel was immunofixation the second being stained for purposes For immunofixation the samples were 30 or 1 40 and 10 or 20 μl thereof were After completion of the focusing 25 μl/cm² of d monospecific antiserum against human serum m or IgA (Dakopatts Copenhagen Denmark) plied to the surface of the polyacrylamide gel at er the area where these proteins are known to be 18) Incubation was carried out at room tem e for 40-60 min The gels were then washed and destained (20)

inidase experiments

sera and pathological patient sera were examined ns of isoelectric focusing and direct immunofixa th antibodies against transferrin after complete ation with neuraminidase (1 U/ml from Vibrio e Behringwerke West Germany) (18) Five μl of were incubated with 40 μl neuraminidase at +37°C hours and diluted with distilled water to 1 20 for ric focusing and to 1 30 and 1 40 for immunofixa

ination of the S GT activity

samples from 89 of the alcoholic patients 19 of the with liver diseases and the eight controls par ng in the experiment with daily ethanol intake (see were examined on the same days as samples for ric focusing were taken The S GT activity was ly determined according to Szasz et al (25) with ts for Technicon SMA 12/60 from Boehringer heim GmbH Mannheim West Germany (Labora of Clinical Chemistry Karolinska Hospital Stock) The reference value of the laboratory was <1 0

nol administration to healthy volunteers

volunteers were all medical personnel at the linska Institute Clinical Department of Alcohol and Drug Research They had abstained from alcohol for one week before the experiments were keeping a normal diet throughout the trial and had agreed not to use alcohol beverages during the experiments

Three healthy males participated in a trial involving ingestion of one single dose of 1 8 g ethanol/kg b wt in the form of Scotch whisky at noon Serum samples for isoelectric focusing were collected on the morning before the trial and on the first and second mornings after ethanol intake

Another eight volunteers participated in an experiment involving daily ingestion of 0 60 g ethanol/kg b wt (95 5% ethanol diluted with pure fruit juice) every afternoon for seven days The daily amount ingested corresponds to about 50 cl wine Serum samples for isoelectric focusing and S GT determination were taken on the morning before the trial from all eight subjects and thereafter every morn ing for 8 days and on the 11th day From two of the subjects with positive results on isoelectric focusing it was possible to collect samples also on the 13th 15th and 18th days

Statistical method

Fisher s exact test was used to compare the frequency of the abnormal transferrin component and increased S-GT activity between the four patient groups The same test was used to make the comparison between the presence of the transferrin alteration and elevated S-GT values within each group

RESULTS

Controls

The normal protein pattern on isoelectric focusing is shown in Fig 1A In only one individual (male aged 32 years) was the transferrin abnormality pres ent which represents 1% in the control material (Table I)

Alcoholic patients

B and F in Fig 1 show the transferrin abnormality after isoelectric focusing and its specific identifica tion with direct immunofixation It consists of a selective and marked increase of a microhetero-geneous component with a higher isoelectric pH (pI 5 7) than the normal main band of this protein (pI 5 4) (21) None of the other six components of transferrin shows any corresponding increase In the serum of the patient shown in the figure there is also a faint additional even more cathodal band at the pI of 5 9 which has been found in one quarter of alcoholic patients (21)

The results from desialylation with neuramini dase of normal and patient sera are exemplified by C–D and G–H in Fig 1 After complete removal of the sialic acid the difference between normal

The 8% positive results for both the transferrin component and elevated S GT activity among patients in group I is probably an expression of unadmitted alcohol intake The slightly but not significantly higher frequency of the transferrin abnormality in group II may have the same cause or be due to a remaining change from higher consumption during the preceding week This may also explain the somewhat but not significantly higher frequency of increased S GT values than the abnormal transferrin band in group II since raised values return slowly to normal levels within 2–3 weeks of abstinence (12) Further the S GT activity may increase after intake of relatively large amounts of alcohol during a short time (3 14)

Some other proteins α_2 macroglobulin haemopexin C'3 complement and IgA have components in close proximity to the abnormal transferrin band and may therefore impose problems if increased (18 20) Direct immunofixation following isoelectric focusing using antibodies against transferrin is then a convenient means to establish the nature of the protein band (Fig 1*E–F*) In some samples lipoproteins may be found in the same region These are usually easy to identify since they focus badly often with the appearance of zig zag bands and are seen on the surface layer of the gel of the type used here In doubtful cases the lipoproteins can be removed quickly by delipidation according to Cham and Knowles (1) (Stibler unpublished)

The cause of the change of the transferrin has so far not been established A purely quantitative explanation has previously been excluded (21) and also contradicted by the fact that the alteration comprises just one component at the position of which there is normally only one of the minor bands of the protein The results of desialylation (Fig 1*G–H*) speak in favour of a reduced sialic acid content in the abnormal component The remaining difference from normal sera after desialylation reported on crossed immunoelectrofocusing (21) may be due to technical difficulties with that method differences in the amount of diffused protein from the polyacrylamide gel to the agarose gel or to errors concerned with the low mobility of proteins isoelectric around pH 6 in the buffer pH used The direct immunofixation technique is more sensitive and more reliable in the present situation since it is not afflicted with these sources of error (20) A low sialic acid content might be due to a defective sialylation by sialyl transferase during synthesis, normal release of newly synthesized but not sialylized transferrin to increased peripheral sialic acid or to a defect in the elimination of acid deficient transferrin (2) Since no corresponding qualitative change has been observed in other glycoproteins studied this defect appears to affect transferrin in a more selective way

Investiations are currently being carried further study the specificity of the transferrin abnormality for alcoholism e g in pat... malabsorption and other types of addiction thermore a method to make possible a quant... estimation of the abnormal component in relation to the main one is being developed

ACKNOWLEDGEMENTS

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Free Light Chains of Immunoglobulins in Amyloidosis

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ACT Monomeric (M) and dimeric (D) forms light chains in serum have been measured by a e radioimmunoassay in eight patients with dosis without monoclonal proteins Signifi elevated concentrations of D lambda chains demonstrated in two of four patients with d amyloidosis The two patients had a sig tly increased D/M ratio of both kappa and a chains One patient with localized amy s and normal concentration of monomeric meric light chains had an abnormal fragment l chains A low kappa/lambda ratio was found ients with localized amyloidosis Four patients econdary amyloidosis and renal insufficiency creased amounts of free light chains The con tion of light chains and the D/M ratio in this corresponded to the impairment of renal func

ords immunoglobulin light chains amyloidosis Med Scand 206 283 1979

oid proteins may be both of immunoglobulin non-immunoglobulin origin (1 4 15) Light s of immunoglobulins are presumed to be one e proteins constituting the amyloid fibrils Jones proteins have been shown to be the e of amyloid fibrils in a patient with plasma yscrasia (14) The source of the amyloid fibrils atients without monoclonal proteins is un n. Kappa and lambda light chains of immuno- ulins or polymeric forms of light chains in a may be of pathogenetic significance In the ent study we have used a sensitive radioim oassay for light chains to investigate the con rations of light chains in eight patients with loidosis

STUDY POPULATION

r patients had localized amyloidosis limited to the iratory tract and no coexisting diseases (3 6 7) r patients had secondary amyloidosis three had amyloidosis secondary to rheumatoid arthritis and one had amyloidosis secondary to tuberculosis (7) Patients with monoclonal proteins on immunoelectrophoresis (Scheidegger) were excluded this method detects monoclonal proteins at concentrations above 1 g/l All patients with primary amyloidosis had serum creatinine below 1 3 mg/100 ml and no proteinuria The patients with secondary amyloidosis had amyloid deposits in *the kidneys with proteinuria and decreased creatinine* clearance

As controls we investigated serum from 11 patients with rheumatoid arthritis (six seropositive four seronegative and one juvenile arthritis) six patients with tuberculosis (three with active tuberculosis and three with previously treated tuberculosis) and six normal individuals

METHODS

The diagnosis of amyloidosis was made on biopsy material The amyloid showed green birefringence with Congo red under polarized light

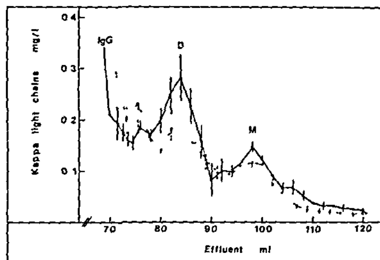
Polymeric forms and split products of free light chains were isolated by gel filtration using a Sephadex G 100 SF column measuring 140×1 5 cm The concentrations of light chains in each fraction were measured by a sensitive radioimmunoassay as previously described (10 11 12) The total amount of monomeric and dimeric light chains was calculated by summation of the respective fractions The molecular weight was estimated by markers of radio-labelled lambda chains Non absorbed broadly reactive antibodies against kappa and lambda Bence Jones proteins were used This was possible because the regular immunoglobulins were separated from the light chains by gel filtration

RESULTS

On gel filtration on Sephadex G 100 the free light chains appeared after intact immunoglobulins in two peaks with molecular weight about 44 000 and 22 000 i e as dimers (D) and monomers (M) (Fig 1) Higher polymeric light chains (tri or tetramers) were demonstrated as a small peak between intact immunoglobulins and dimeric light chains The total

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Abbreviations M = monomeric light chains D dimeric light chains



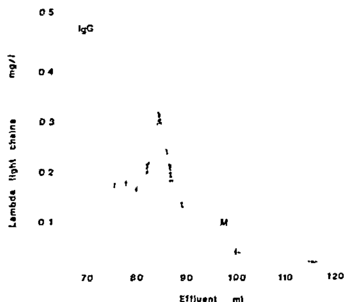


Fig 1 Mean values of kappa and free light chains after gel filtr Sephadex G 100 SF in four pati localized amyloidosis (—) and six individuals ( ) Vertical lines standard error

mount of dimeric and monomeric kappa and lambda light chains in serum is shown in Table I

In the group with localized amyloidosis two of the four patients had elevated concentrations of D lambda chains when compared to normals (*t*-distribution) All patients had normal concentrations of kappa chains and M lambda chains The concentrations of the tri or tetrameric chains could not be precisely quantitated due to contamination of intact immunoglobulins Patient 4 with normal concentrations of M and D light chains had a small abnormal peak appearing after the M light chains (Fig 2) This peak represents fragments of kappa and lambda light chains

Two patients (nos 2 and 3) had significan vated D/M ratio of both kappa and lambda c The mean D/M ratio of kappa chains in loc amyloidosis was 1 6±0 5 (S D) compar 1 2±0 2 (S D) in the six normal individu mean D/M ratio of lambda chains was 3 (S D) compared to 2 7±0 7 (S D) in the individuals Both these differences are not (Mann–Whitney rank sum test) The kappa ratio in localized amyloidosis was 0 87 compa 1 05 in the six normal individuals The differe not significant (Mann–Whitney test)

Patients with secondary amyloidosis had s cantly increased mean values of kappa and la

Measu emen s of M and D free l gl t cl ns (Lc) of l bd ι ι d k pp ι type in 4 pat e ts tl dom l dos s and n 4 pat ents ith sec dar a l los s

	Pat no	Kappa Lc (µg/ml)				Lambda Lc (µg/ml)			
		M	D	M+D	D M	M	D	M+D	D M
d	1	4 1	5 6	9 7	1 4	2 9	6 8	9 7	2 4
		3 6	6 7	10 3	1 9	1 8	10 7	12 5	5 9
	3	4 1	8 1	122	2 0	3 0	13 3*	16 3	4 4
	4	2 9	2 6	5 5	0 9	1 1	3 4	4 5	3 1
		3 7	5 8	9 4	1 6	2 2	8 6	10 8	3 9
		0 6	2 3	2 8	0 5	0 9	4 4	5 0	1 5
ry	5	17 6	19 1*	36	1 1	2 9	17 4	20 3	6 0
	6	9 7	10 1*	19 8	1 0	1 4	15 4	16 8	11 0
	7	12 0	18 9*	30 9	1 6	2 8	33 4	36 2	11 9
	8	6 6	8 7*	15 3	1 3	1 6	8 2	9 8	5 1
		11 5*	14 2*	25 7	1 3	2 2	18 6	0 8	8 5*
		4 6	5 6	9 8	0 3	0 8	10 6	11 1	3 4
f6 normal		3 7	4 5	8 2	1 2	2 1	5 7	7 8	2 7
		0 9	1 4	2 3	0 2	0 7	1 6	2 1	0 7

x

in serum (Mann-Wh tney rank sum test) n entrat ons of kappa and lambda cha ns in were n ersely correlated to the creat n ne ae Bo h M and D kappa cha ns were ele whe eas only D lambda cha ns were elevated e of four pat ents The D/M ratios of kappa mbda chains we e 1 3+0 3 (S D) and 8 5+3 4

The correspond ng values in anephric pa were 1 0+0 3 and 6 9+3 4 (S D) (10 11) d fferences are ins gn f cant The kappa/ a rat o was 1 24 and d d not d ffer sign f cant n normal

mean value of free kappa l ght cha ns in 11 s with rheumato d arthritis was 10 2±4 2 µg/ml serum and of lambda chains 6 6+2 3 µg/ml One pat ent w th rheumato d arthrit s creased values of both kappa and lambda and one pat ent had ncreased values of only chains

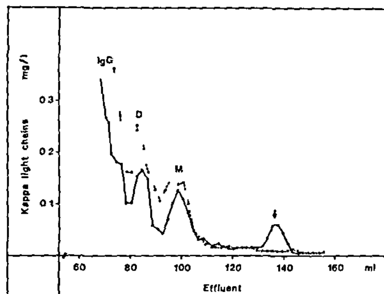
a ents w th tuberculos s had normal values value of kappa l ght chains 10 1+3 5 (S D) serum and of lambda cha ns 7 1+ 1 3 (S D) None of the mean values d ffered s gnif cant n normal values (Mann-Whitney rank sum

DISCUSSION

s udy we have demonstrated elevated con tions of lambda l ght cha ns in two of four pat ents with local zed amyloidos s None of the pat ents had monoclonal immunoglobul ns detect able by immunoelectrophores s (Sche degger) Chem cal stud es have shown that the ma n prote n component of purif ed amylo d f brils in primary amylo dosis and local zed amylo dosis is a whole l ght chain or the am no term nal variable fragment of a l ght cha n (4 5 7 9) Thus circulating l ght cha ns of immunoglobul ns may be of pathogenet c s gn f cance in the depos t on of amylo d f brils in pr mary and local zed amylo do is Free l ght cha ns have however never before been measured in serum from pat ents with primary and local zed amylo dos s probably due to the rather insensitive methods generally used for measurements of l ght cha ns

Glenner and Page (4) isolated from a pat ent with primary amylo dos s a serum protein w th ant gen c determinants in common w th both amyloid f brils and lambda Bence Jones protein The concentration of th s serum prote n was est mated to be less than 0 1 mg/ml and the molecular we ght about 90 000

The demonstrat on of such small amounts re qu res a sensitive rad oimmunoassay The detect on l m t for our a say is 0 002 mg/l On gel filtrat on we found that the lambda and kappa cha ns were eluted correspond ng to intact free l ght cha ns with molecular we ghts of about 22 000 and 44 000 Fragments of l ght chains were detected n only one pat ent (no 4) In the depos ts however ntact l ght



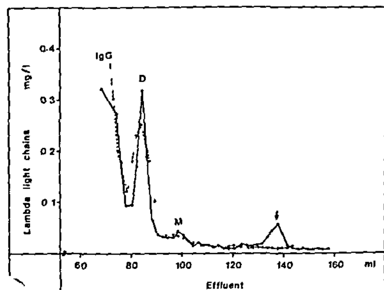


Fig 2 Measurements of kappa and l ght cha ns after gel filtration on Se G 100 SF in a pat ent with lo amylo dos s The arrow shows an ab peak of l ght chain fragments

as well as fragments of light chains have been demonstrated (14)

In patients with localized amyloidosis the mean D/M ratio of kappa chains was 1 6 compared to 1 2 in normal sera For lambda it was 3 9 compared to 2 7 in normal sera The values are not significantly different from normal probably due to the small number of patients Two patients (nos 2 and 3) however had increased D/M ratios of both kappa and lambda chains This is suggestive of an increased polymerization rate in localized amyloidosis (Fig 1) The amount of tetrameric lambda light chains was accentuated in patients with localized amyloidosis but precise quantitation was not possible due to contaminat on of gel immunoglobulins The ratio kappa/lambda cha was 0 87 i e a relatively higher increase in lam than in kappa chain concentration This is t opposite of normal sera (10) but the difference not significant probably due to the small num of patients Elevated polymeriza ion rate and t elevated concentration of lambda chains ma elevated plain why lambda chains are most often encount ered in amyloid deposits (4)

An abnormal polymer of kappa chains has be demonstrated in another patient (13) Interesting this patient had nodular glomerulosclerosis wi deposits of kappa chains detected by imm

nce Staining reactions for amyloid were Thus deposition of light chains does not ily lead to amyloidosis

ients with secondary amyloidosis the mean f both kappa and lambda chains were ele This is correlated to impairment of renal We have previously demonstrated an in rrelation between the concentration of free ins and the glomerular filtration rate (11) centration of light chains and the D/M ratio iffer significantly from the values observed nts with similar renal insufficiency of other Thus elevated concentrations of light o not per se lead to amyloid deposits

of 11 patients with rheumatoid arthritis had l values of light chains without any sign of osis The significance of these findings is nown A similar frequency of elevated light e rheumatoid arthritis (2 of 40 patients) has scribed by Epstein and Tan (2) All patients berculosis had normal values for light Thus prolonged stimulation of the immune does not necessarily lead to increased light oncentration This is in agreement with the that secondary amyloid proteins have a component of non immunoglobulin origin

ACKNOWLEDGEMENT

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Prognosis in Hypertrophic Obstructive Cardiomyopathy

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ACT Thirty-eight non-operated patients ypertrophic obstructive cardiomyopathy) were followed for 1-18 years (mean 8) patients died, nine of them instantaneously any other apparent cause of death The es on the first admission did not discriminate those who died and those who survived dur observation period nor did the findings at atheterization at rest or left ventricular an iography However, cardiac enlargement on chest X ray was significantly more common eceased group 75% against 27%, as was the e absence of a q-wave in lead III on the first 3% against 42% The combination of com ck of q in lead III and cardiac enlargement on -ray at the initial examination was present in 12 deceased (75%) and in only 3 of 24 sur- (13%) This can be used to select patients for rm prophylaxis against ventricular fibrillation according to the literature, is the main mech of instantaneous death in HOCM

rds hypertrophic obstructive cardiomyopathy es

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lity in hypertrophic obstructive cardiomyo- (HOCM) is high the estimated ten year figure 35% (7) Most deaths are sudden (7) and more due to arrhythmias than to obstruction (6) an ECG was recorded immediately after a se in five HOCM patients ventricular fibrilla VF) was found in all (11) Twenty four hour latory ECG monitoring revealed paroxysmal icular tachycardia in 16 of 70 HOCM patients wo of these 16 patients died suddenly during ext two months (14) Otherwise sudden death s to have been unpredictable in HOCM efore the main purpose of this follow up study n-operated HOCM patients was to find pre rs of death and especially of instantaneous 1.

PATIENTS AND METHODS

In 1960-77 HOCM was diagnosed here in 40 patients who were not treated surgically Two of the patients could not be traced at a follow up study in 1978 Of the remaining 38 patients 26 were males and 12 females aged 13-65 years (mean 38) when first seen here

The patients were examined by left and right heart catheterization and left and/or right angiocardiography The diagnosis of HOCM was based on a left and/or right ventricular outflow tract gradient at rest of >5 mmHg either spontaneously or following a premature beat or by isoprenaline provocation and/or angiocardiographic evidence of encroachment of the ventricular cavities by the interventricular septum or in the left ventricle the anterior leaflet of the mitral valve

RESULTS

During the 1-18 years (mean 8) that the 38 patients were followed 12 (32%) died The estimated mortality was 22% at five years and 58% at ten years

In ten of the deceased patients HOCM seemed to have been the main cause of death The cause of death was obscure in the other two one of whom developed frank pulmonary edema and hypotension during gastrointestinal bleeding and blood transfusion and the other died instantaneously and the autopsy disclosed advanced coronary arteriosclerosis In one of the ten patients who died from HOCM the cause of death was cerebral emboli Three of the remaining nine developed increasing symptoms of heart failure on effort before death but died instantaneously In the other six patients the death was unexpected and instantaneous Thus totally nine patients without cardiac symptoms at rest died instantaneously without any other known cause than HOCM Two of the latter patients were on β blocking drugs compared with seven of the 26 survivors ($p>0.05$)

Abbreviations HOCM=hypertrophic obstructive cardiomyopathy VF=ventricular fibrillation PWC pulmonary capillary wedge pressure

Table I *Symptoms ECG patterns and findings at left ventricular angiography on first admission in 26 survivors and 12 non survivors*

None of the differences between deceased and survivors is significant ($p>0.05$)

	Deceased (%)	Survivors (%)
Symptoms		
Dyspnea	67	38
Chest pain	50	38
Palpitations	33	19
Syncope	8	23
ECG pattern[a]		
Delta waves	8	0
Abnormal Q waves	42	25
Left ventricular hypertrophy	50	50
Left ventricular angiography		
Encroachment of the left ventricular cavity by the interventricular septum and/or the anterior mitral leaflet	90	64
Mitral incompetence	40	24

[a] Criteria delta waves ≥0 03 sec abnormal Q waves ≥0 04 sec LVH R in V5/CR5 >27 mm or R in V5/CR5 + S in V1/CR1 >35 mm and ST T depression in V5/CR5

Besides the 12 deaths during the observation period one patient was resuscitated from VF Two other patients developed syncope and second or third degree AV block Although asystole was not recorded it is the most probable cause of their syncope The initial ECG in one of these two patients showed left anterior hemiblock plus right bundle branch block The other patient had no conduction defect when first seen but had a left bundle branch block when admitted for syncope Both these patients received pacemakers and another two were being paced when first seen Only two of these four patients could be paced from the atria Both are alive as is one of the two with ventricular pacemakers

The incidence of proven HOCM in first degree relatives as well as suspected HOCM (sudden death or heart disease at early age) was 22% There was no difference in the familial incidence between non survivors and survivors (both 44%)

Some of the symptoms on the initial admission are shown in Table I The cause of palpitations was atrial fibrillation in all with documented arrhythmia

All the 38 patients had a systolic murmur o tion type when first seen Delayed onset (as ured on phonocardiogram from fourth le costal space in the 100 Hz channel) occur about 60% of both those who survived a who did not

Heart volume on the initial chest X-ray erect position (8 12) was increased sign more often among the deceased 75% agai ($p<0.01$)

Some ECG patterns commonly descri HOCM are presented in Table I as they occ the first recording Two patients had paced and the ECG could be evaluated in only 36 p

When the first ECG of the deceased a survivors were compared the deceased wer to lack a q wave of any amplitude in lead I often than the survivors (10 of 12 against 1 $p<0.05$) The two deceased with a q in III only two among the dead patients with a r figuration in aVL while this QRS pattern o in only one of the 14 survivors with a q ($p<0.05$)

There was no significant difference betw tients with and without q in III with regard QRS axis occurrence of fascicle/bundle blocks left ventricular hypertrophy or abn waves in precordial leads The three patie rSr in aVL (and q in III) were all aged 17 all the other three patients below age 22 ha in III These three patients with rSr in aVL to have a more vertical mean QRS axis th remaining 31 patients but the difference significant (80° against 15° $p>0.05$)

The only association with the lack of a was an increased heart volume at chest X ra 15 against 8 of 21 $p<0.05$) rSr in aVL w seen together with normal heart volume combination of no q in III *and* increased he ume was present in 9 deceased and 3 sur while rSr in aVL *and* normal heart volum found in 2 deceased and 1 survivor Thus series combining these two criteria woul correctly predicted 11 of 12 deaths and predicted four of 24 survivors All the stantaneous deaths from HOCM were amon predictable deaths Four of these 11 deaths red within one year six within three and all 12 years The two patients who developed Stokes attacks during the observation peri not among the four with wrongly predictable

Findings at the heart catheterization on admission

the differences between deceased and survivors ...ant ($p>0.05$)

	Deceased (%)	Survivors (%)
...upine		
...d cardiac output (relative ...uptake regression line – ...)	17	8
...ncular outflow tract (>5 mmHg) spontaneously ...inus rhythm	75	46
...postectopic beat and/or ...soprenaline infusion	85	54
...tricular outflow tract (>5 mmHg) spontaneously ...inus rhythm	17	27
...postectopic beat and/or ...soprenaline infusion	17	31
...d left ventricular end ...pressure (>13 mmHg ...0)	92	77
...d right ventricular end ...pressure (>8 mmHg ...0)	58	54
...ycle exercise supine		
...ed cardiac output (relative ...uptake regression line – ...)	50	50
...ed PCWP ...e cardiac ...regression line ...D) (%)	100	95

...left ventricular angiocardiography on the ...mission did not show any significant differ... ...etween the deceased and the survivors (Ta...

...heart catheterization on the first admission ...a tendency for more severe results in the ...ed group but there were no significant differ... ...at rest (Table II)

...of the patients had a left and/or right outflow ...radient at rest spontaneously or on provoca... The left ventricular gradient was significantly ...r among patients with radiologically in... ...d heart volume (in the erect position) than ...normal heart volume 40 against 14 mmHg ...01)

...pulmonary capillary wedge pressure (PWC) ...nted in relation to cardiac output in Fig 1 ...est PWC value among the deceased during

Fig 1 PWC in relation to cardiac output ($\dot{Q}$) in supine position at rest and during bicycle exercise ——= Regression line in normal individuals – – – = +2 S D (2)

exercise was 23 mmHg only 55% of the survivors reached this figure ($p<0.05$) Only one of the four patients with wrongly predictable death fell below that borderline

DISCUSSION

Although this series differs from other series in that it does not include any children or any patients treated surgically the annual mortality 4% is rather similar to the 3 5–6 6% in four other studies (1 5 7 10) The proportion of sudden deaths is also similar in these five series 50–63% (1 5 7 9)

In this series no difference was found in outflow tract gradient of the left ventricle at rest between deceased and survivors nor in left ventricular end diastolic pressure at rest as was similarly reported by (9) It has been suggested that the left ventricular outflow tract gradient may decrease with age (7) That was not the case in this series The gradient was 20 mmHg in patients below 40 years and 32 mmHg above ($p>0.05$) Although the heart volume in the erect position also tended to increase with age (454 ml/m² BSA below 40 years and 515 ml/m² above $p>0.05$) patients with enlarged hearts had significantly greater outflow tract gradients in the left ventricle (400 mmHg against 14 mmHg $p<0.01$) Frank and Braunwald (5) also found greater gradients in patients with moderate or marked enlargement compared to patients with normal or slightly enlarged hearts The cardiac enlargement may be caused to some extent by left ventricular hypertrophy but in the two cases with the outstanding enlargement (both 800 ml/m² BSA) the left ventricular outflow tract gradients were also rather

high 60 and 44 mmHg. These large heart volumes corresponded to dilated left ventricles on the angiocardiogram and both patients had symptoms of heart failure. These findings do not support the view that the gradient decreases as the myocardium fails.

Frank and Braunwald (5) found slight cardiac enlargement on chest X ray in 29% and moderate or marked enlargement in 41%, making a total of 70% of their patients, compared to 42% in the present series. The heart volume (in the prone position) is also increased in relation to total hemoglobin in HOCM (3). The prognostic value of that relation has been noted in a small series (13) but in the present material the heart volume did not discriminate better when related to total hemoglobin.

The frequent lack of a q of any size in lead III in the deceased group might have several explanations. A different position or configuration of the heart as measured by the mean QRS axis was not the cause, nor were intraventricular conduction disturbances. As the hearts were often radiologically enlarged, a generalized hypertrophy and/or dilatation may contribute to the absence of a q in III although the left ventricular hypertrophy pattern in the ECG was not present to a significant degree. An abnormal septal anatomy/activation is another possible explanation but positive support is lacking.

The figures behind the predictive value of rSr in aVL are so small that, although statistically significant, no conclusion ought to be drawn from them. However, rSr may be the equivalent in young patients with small vertical hearts to the lack of q in III in patients with enlarged and more horizontal hearts.

As VF seems to be the main mechanism of instantaneous death is HOCM patients, the consequence of finding a high risk of such death might be to give the patient long term drug prophylaxis against VF. A serious side effect of antiarrhythmic drugs is a prolonged asystole if complete AV block supervenes. In this series, however, neither of the two patients developing high degree AV block and Adams Stokes attacks had the findings predictive of instantaneous death.

CONCLUSION

At the first examination in HOCM patients, the combination of a complete lack of a q wave in lead III and any degree of cardiac enlargement on X ray indicates a high risk of instantaneous death during the next few years.

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Myocardial Infarction in Malmo during the 10 Year Period 1963–1972

Sven Olof Isacsson and Bengt W Joh nsson

F on he Hea Sec n Depa n ent f In ern l Me l ne Ce er l H p t l M l S eden

ICT Myocard al infarct ons in Malm o dur 10- ear period 1963–72 have been studied tali from myocard al infarct on decreased n l among men during th s period but not women The ncidence of hospital treated in increased sign f cantly among men ma nly n nc ease in primary infarctions The one n al in this ho p tal material did not im brm the period The number of days of re during 12 months before primary infarc is sign f cantly h gher than expected The n of s ck lea e during the year after primary on remained unchanged throughout the The mortal ty f gures relate to all age groups sing 2111 men and 1409 women The hospital te relates to men and women aged 65 years or and compr ses 1323 men and 279 women dur period concerned The reduced mortal ty and ed ncidence of hosp tal treated infarction are ly expla ned by the fact that more men seek l treatment lead ng to a better prognosis The ura on of sick leave after infarct on is prob ue to causes other than strictly medical factors

d myocard al nfarct on morb d ty mortal ty led Scand 06 93 1979

s on he prognos s after myocard al infarction mainly dealt w h the annual mortal ty (1 3 6 19 73 9) and the pat ents ab l ty to return to (4 (1 2 74 5) The pat ents state of health g he years after myocard al infarction has also s ed (7)

have endeavoured to eluc date certa n other ts of myocard al infarct on and have stud ed lar t ends n several variables over a 10-year d n a def ned population The variables ed are mortal ty from infarct on in the total la on nc dence of hosp tal treated infarct on ar surv val n the hosp tal treated patients and s ck leave dur ng the year before and after onset of infarction

PATIENTS AND METHODS

The study comprises 1373 men and 279 women aged 65 years or below who were adm tted to the Department of Med c ne Malmo General Ho p tal dur ng the period Jan 1 1963 Dec 31 1972 Th s is the only ho p tal for treat ment of acute cases in the city and w th few except ons all pat ents w h acute myocard l infarct on n Malmo are treated n our department Of the 13 3 men 1061 are presented as primary infarct ons 189 had two infarct ons and 57 three or more S xteen men evenly d stributed o er the 10-year period were excluded ow ng to incom plete data Of the 279 women 217 had pr mary infarct ons 43 had two infarct ons and 6 three or more Th ee women were excluded ow ng to ncomplete nformat on The re sults are ma nly restricted to nd v duals aged 64 years or below and n erest s focused on pat ents w th primary nfarct ons

The d agnos s of nfarct on has been based on r es n transaminase ECG abnormal t es and chest pain (9) In format on on number of days of s ckness benef t and d s ab l ty pens ons has been obta ned from the Nat onal In surance Off ce The s ckness index i e the number of days of s ckness benef t ent tlement per person per year has been calculated for each nd v dual n the same way as n the stat st cs regula ly issued by the Nat onal Insurance Off ce Pat ents who have ret ed or moved out of the d strict have been excluded from the calculat ons of the s ckness ndex

The date of death of those who have d ed has been determ ned in order to calculate surv val after infarct on The total morta ty from myocard al nfa ct on n the C y of Malmo wh ch has been calculated for all ages is based on the ICD code fo myoca d al nfarct on accord ng to the death cert f cates as calcul ted by the Swed sh Cen tral Bureau of Stat st cs wh ch scrut n zes all death cert f cates issued n Sweden Informat on about the nc dence of post mortem exam nat ons n the c ty has been obta ned from the Department of Pathology Malmo General Hosp tal

Age-spec f c prevalences have been calculated per 100000 nhab tants for each age group The s at st cal calculat ons have ma nly comprised tests for trend n con t ngency tables wh ch perm t assessment of any s gnif cant changes ncreases or decreases during the 10-year period



Fig 1 Number of deaths from myocardial infarction per 100 000 45–64-year-old men in the City of Malmö in 1963–72

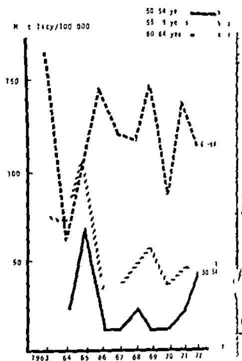


Fig 2 Number of deaths from myocardial infarction per 100 000 50–64 year-old women in the City of Malmö 1963–72

RESULTS

Mortality from myocardial infarction

The total mortality from myocardial infarction based on death certificates for men aged 45–64 years is shown in Fig 1 and for women aged 50–64 years in Fig 2 A significant reduction in mortality ($p<0\ 05$) was found among men in the age groups 35–39 45–49 55–59 and 60–64 At age [illegible] and above the reduction is somewhat more pronounced ($p<0\ 01$) No corresponding change could be demonstrated among women during the period

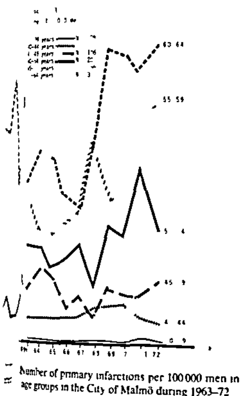
During the 10-year period 2111 deaths due to myocardial infarction were recorded among men and 1409 among women living in the City of Malmo 35% of the men and only 13% of the women died before the age of 65 years The incidence of autopsies on which the death certificates were based remained constant at about 90% throughout the period at the ages concerned

Incidence of hospital treated infarction

The total number of infarctions during the 10-year period and the proportion of primary infarctions in each age group are shown in Table I The change in incidence of infarction during the 10-year period in the various age groups for men up to 65 years [illegible] completely explained by the increase in primary infarctions shown in Fig 3 No increase in the incidence of two or more infarctions during the period could be demonstrated A significant increase in primary infarctions was found for men in the age groups 0–39 ($p<0\ 01$) 50–54 ($p<0\ 05$) [illegible]

Table I Total number of myocardial infarctions and proportion of primary infarctions by age and sex during the 10 year period

	Women		Men	
Total no of infarctions	279		1 323	
Of which primary infarctions in the age groups				
0–39	2	217 (77 8%)	28	1 061 (80 2%)
40–44	5		55	
45–49	9		106	
50–54	24		202	
55–59	61		296	
60–64	101		337	
65	14		37	



Number of primary infarctions per 100 000 men in age groups in the City of Malmö during 1963–72

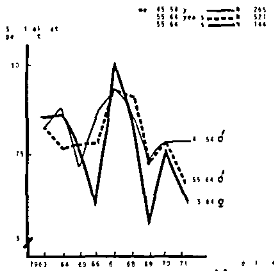


Fig 4 Proportion of men and women still alive 1 year after first admission to hospital for myocardial infarction in the City of Malmö 1963–71

...01) and 60–64 ($p<0$ 01) For women there is ...sistent pattern the number of primary infarc... in the different years is relatively small When ...roups 0–39 and 40–44 years are pooled a ...cant increase ($p<0$ 05) did occur during the ... but the total number of infarctions in these ...oups was only seven

...ear survival among 45–64 year old men with ...rdial infarction treated in hospital

...mortality including hospital mortality and ... after discharge calculated from the date of ...sion to hospital is shown as the one year ...ed in Fig 4 The figures relate to the two ... 10-year classes of men 45–54 and 55–64 ... No significant change during the period could ...emonstrated There is no trend towards an in... ...ed proportion of survivors the curves are ...st identical for the two age groups with 67– ... still alive after one year There is some drop- ... owing to patients moving out of the district ... ng the period but the figures are constant and ... throughout the period only about 0–3 individu... ...er year in the various age groups ($N=786$ 22 ...uals)

Sick leave during the year before the first infarction

Figs 5 and 6 show the morbidity expressed as the observed number of days of sick leave during 12 months before the first infarction The figures are compared with the expected number of days of sick leave i e the mean value for the age groups for the whole city The figures relate to the age group 50–59 where the excess morbidity was high est with a sickness index 1 8 times higher than expected in men (46 days compared to 26 days

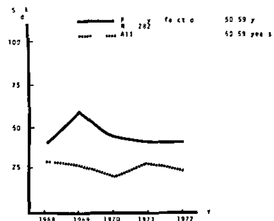


Fig 5 Number of days of sick leave during 12 months (sickness index) before infarction in men with primary infarctions compared to all men of the same age in the City of Malmo 1968–72

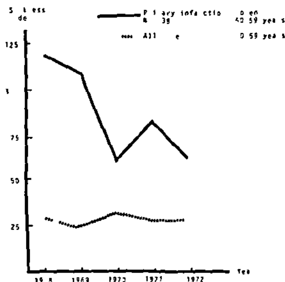


Fig 6 Number of days of sick leave during 12 months (sickness index) before infarction in women with primary infarction compared to all women of the same age in the City of Malmö 1968–72

expected sick leave) and 3 times higher than expected in women (86 days compared to 29)

Sick-leave during the year after primary infarction

In order to obtain at least a rough measure of the burden on the community caused by myocardial infarction over a period the average number of days of sick leave per individual during 12 months after primary infarction has been calculated for individuals who were still alive at the end of one year and had not moved from the city or retired Fig 7 shows the figures for men in the age groups 45–54 out of 215 included 6 moved or retired) and (362 out of 408 survivals included 46 moved or retired) It is obvious that the infarction patients as a group did not change during the period The age difference of 10 years between the groups seems to have had a negligible influence on the number of days of sick leave

DISCUSSION

Myocardial infarctions in Malmo have previously been analysed in various contexts (2 3 9 10 21)

The reduced mortality from infarction during the period studied in this investigation may be due to various causes Altered classification is one possibility The cause of death is based on death certificates The incidence of autopsies in M however very high about 90% through period in the relevant ages It is therefore that altered classification contributed to the tion A reduced incidence of infarction changed mortality would also explain the A reduced incidence of fatal infarction with change in the total incidence of infarction is possible explanation Such a change might for example to changes in the risk factor The fact that the reduction only involves gests however that the change is not expl altered classification but is due to a true de mortality from infarction caused by facto than cohort effects A reduction in mortal infarction has also been found in other co recent years particularly in the USA An incidence of hospital treated myocardial has previously been reported from Malmö period 1935–68 (2 9) The authors were opinion that the increase cannot be expl diagnostic criteria alone or by an increased cy among patients with myocardial infa seek hospital treatment but is due to a true in incidence Our study population shows trend If the increase in incidence is consi an isolated phenomenon a true increase population altered diagnostic criteria and

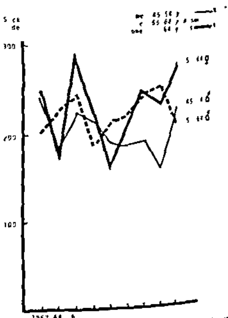


Fig 7 Number of days of sick leave (sickness ... during the first 12 months after primary infarction ... and women in the City of Malmo 1961–71

·y among patients with chest pain to seek treatment are all factors which separately ·nbination might contribute to the increase ·al treated myocardial infarctions

ne year survival in the hospital treated pa ·s not changed significantly during 9 of the studied The one year survival during the ·r after discharge from hospital has been · in several publications (1 3 8 11 19 23 ·as the mortality during hospital stay (14 15 In a study from Gothenburg Sweden ·al (23) found that 87% of men and women ·mary infarction were alive one year after i e 13% had died Reinfarction in the mortality to 37% during the first year ·ed sh cooperative CCU study (7) the total mortality was 10% at the age of 39 and ·d rose to 20% at the ages of 60–69 years ·U in Malmo was established in 1968 in the ·f the period covered by this study The · among our study population during the ·t is essentially the same as in other Swedish We found no trend towards increased during the 10-year period The individual ·ng thus does not seem to have decreased ·e study period in this hospital material

·bservations show that there has been a ·nt reduction in mortality from infarction ·en during the 10-year period at the same ·he incidence of hospital treated myocardial ·n has risen significantly mainly due to an ·in primary infarctions The one year has not changed If the incidence of ·al infarction was in reality unchanged dur ·eriod the most likely explanation of our ·ions would be that an increased number of ·ls had been treated in hospital because of ·ial infarction and that the mortality is lower ·hose treated than among those not treated ·al This explanation seems reasonable To ·ther way hospital treatment of myocardial ·n is definitely superior to other forms of ·it The influence of treatment in the CCU ·e assessed in this material We should also ·t that in practice patients with diagnosed ·ial infarction are not treated in their homes ·n It is known that myocardial infarction is ·ceded by a period of increased morbidity ·and Lundman (7) found a history of angina ·in 45–60% of patients with myocardial in mainly primary aged below 69 years (7) Hypertension and diabetes were also more preval ent than expected The same authors also dem onstrated a significantly higher prevalence of hypertension and diabetes as well as of angina pectoris in the histories of women than of men We found a definite increase particularly among wom en in the number of days of sick leave during 12 months before primary infarction This observation is naturally an expression of an increased morbid ity probably angina pectoris hypertension and diabetes as contributory factors although other causes are also possible

Rehabilitation after myocardial infarction has attracted much interest in recent years (5 12 17 18 20) The main reason is the possibility of pro moting the patient s return to work The time be tween onset of infarction and return to work differs however enormously between studies from differ ent countries Only 17% of men with infarction aged 67 and below in a Swedish study (27) were working after 3 months 63% after 12 months and 70% after 24 months In a Danish study (13) 80% of surviving patients had resumed work within 3 months after discharge from hospital In a study from Norway (22) only 40% of men had returned to work at the time of follow up 2–4 years after dis charge A major factor in that study was the ex tremely low proportion 9% of poorly educated men from rural areas who had returned to work Similar findings are reported in a study from Fin land (24) All these studies are from the Nordic countries and are fairly comparable with respect to age

The tendency to resume work evidently depends on a number of circumstances including socio-economic factors Differences between coun tries are probably due to differences in health insurance systems rather than differences in re habilitation It is therefore difficult to compare the burden on the community caused by myocardial infarction in different countries During a period of relative stability on the labour market and only minor changes in health insurance benefits more intensive rehabilitation should influence the dura tion of sick leave after infarction This was not so in our material As a group patients with myocardial infarction were sick listed to the same extent at the beginning and end of the period The greatly in creased interest in active treatment during the acute phase of infarction during the 1960s is thus not reflected by more active occupational rehabilita

tion To judge from the studies of Kjoller (13) and Weinblatt et al (25) most infarction patients seem to be able to resume work within 3 months In the City of Malmö the duration of sick leave remained long throughout the 10-year period studied Medical factors are probably of minor importance for the long duration of sick leave

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Dobutamine in Left Heart Failure after Acute Myocardial Infarction

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ICT Dobutamine a new positive ino-
mg was given as i v infusion at a rate of
µg/kg min to nine male patients with a mod
evere left heart failure The patients were
n our CCU for acute myocardial infarction
nd had PEP/LVET above 0 40 on routine
ions of systolic time intervals PEP (preejec
se) PEPI (PEP corrected for heart rate),
left ventricular ejection time) and LVETI
corrected for heart rate) Dobutamine in
contractility measured as shortening of PEP
I and also increased ejection fraction, meas-
PEP/LVET Concomitantly heart rate in
significantly but no changes were noted in
r diastolic BPs The positive inotropic effect
amine was thus accompanied by a positive
opic effect which limits the usefulness of the
patients with recent AMI

's dobutamine acute myocardial infarction left
re non-invasive parameters

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s a lack of clinically useful positive ino-
rugs Digitalis glucosides have their given
therapy but there is a need for more potent
The drugs in general use include iso-
e noradrenaline and dopamine Their use
iated with well recognized disadvantages
: drugs are chronotropic arrhythmogenic
nge the peripheral resistance To overcome
sadvantages dobutamine was synthesized
shown in animal experiments to selectively
: myocardial contractility without inducing
nia, tachycardia or significant changes in
or mean aortic perfusion pressures (8)
study was performed to assess the effects of
nine on myocardial performance as meas
' systolic time intervals in patients with
impaired cardiac function after recent acute
dial infarction (AMI)

PATIENTS AND METHODS

Nine men mean age 58 years treated in our CCU for AMI were investigated 5–17 (median 7) days after hospitalization for AMI Patients who on routine recordings of systolic time intervals showed impaired cardiac function who were not on digitalis or β receptor blocking drugs and who received maximally 40 mg of furosemide (or a comparable diuretic) were included in the study

After 30 min rest an i v infusion of dobutamine was given using a constant rate infusion pump The drug was diluted in 5% dextrose and given at a rate of 2 5 5 0 and 7 5 µg/kg/min during 30 min at each concentration The systolic time intervals heart rate and BP—measured by brachial artery catheterization—were registered twice during the pretreatment period after 15 and 30 min on each dose and 15 and 30 min after the infusion

The systolic time intervals were registered according to Weissler and Garrard (10) simultaneously with recordings of ECG phonocardiogram and carotid pulse The values registered were preejection phase (PEP) corrected for heart rate (PEPI) left ventricular ejection time (LVET) corrected for heart rate (LVETI) and PEP/LVET Patients with PEP/LVET above 0 40 were included in the study Infusion was discontinued when no further improvement in cardiac performance could be registered or if side-effects like severe palpitations registered tachycardia or other severe arrhythmias supervened

The paired *t* test was used to evaluate intraindividual changes in the registered parameters

RESULTS

One patient was investigated for only 15 min at 2 0 µg/kg/min The concentration and duration of infusion for the other patients were 5 µg/kg/min for 30 min in three 6 µg/kg/min for 30 min in one 7 5 µg/kg/min for 15 min in two and 7 5 µg/kg/min for 30 min in two patients The concentrations of 2 0 and 6 0 µg/kg/min were due to a methodological

---

Abbreviations AMI = acute myocardial infarction CCU = coronary care unit BP = blood pressure PEP = pre ejection phase PEPI = PEP corrected for heart rate LVET = left ventricular ejection time LVETI = LVET corrected for heart rate VEB = vetnricular ectopic beat

Table I *Patient data and effect of different doses of dobutamine on PEP/LVET*

Pat no	Age (y)	Days after AMI	Pre therapy	2 5 µg/kg/min		5 µg/kg/min		7 5 µg/kg/min		Posttherapy		[illegible]
				15 min	30 min	15 min	30 min	15 min	30 min	15 min	30 min	
1	51	8	0 44	0.53	0 50	0 47	0 45	0 38	0 41	0 41	0 49	[illegible]
2	51	11	0 42	0 46	0 39	0 37	0 46	0 38	0 41	0 38	[illegible]	[illegible]
3	72	7	0 47	0 40 (2)	0 40 (2)	0 40	0.36 (4)	0 34	0 38 (6)	–	–	[illegible]
4	54	17	0 46	0 36	0 38	0 33	0 34	–	–	0 46	[illegible]	[illegible]
5	61	9	0 45	0 42 (2)	–	–	–	–	–	0 34	0 39	[illegible]
6	49	11	0 40	0 30	0 29	0 31	0 32	–	–	0 41	[illegible]	[illegible]
7	59	8	0 50	0 41	0 35	0 41	0 35	0 40	–	0 47	0 46	[illegible]
8	63	8	0 37	0 37	0 33	0 30	0 32	0 28	–	0 32	[illegible]	
9	62	5	0.50	0 41	0 44	0 38	0 41	(0 25)	–	0 45	0 45	[illegible]
Mean	58	9	0 45	0 41	0 39	0 37	0 38	0 34		0 41	[illegible]	[illegible]

*$p<0.05$ * *$p<0.001$

error PEP/LVET was reduced in all patients 12–28% (mean 23) suggesting improvement of myocardial function (Table I) The change from pretreatment values is significant The PEP/LVET had again increased significantly 15 min after infusion and no further increase was noted 30 min after infusion Heart rate increased significantly during infusion but no changes were noted in systolic and diastolic BP (Figs 1 and 2)

The positive inotropic effect of dobutamine is also reflected by a significant shortening of PEP and PEPI (Fig 3) No changes were noted in LVETI (Fig 4) Three patients complained of palpitations during infusion Four patients had ventricular ectopic beats (VEB) and two multiform ventricular beats during infusion One patient developed a fall in BP from 140/85 to 100/60 mmHg No other serious side-effects were noted Blood laboratory tests were made before and after infusion and no changes [illegible] found in aminotransferases electrolytes [illegible]um creatinine or WBC

DISCUSSION

Patients with myocardial infarction complicated by severe left ventricular failure present a major therapeutic dilemma Positive [illegible] like dopamine noradrenaline [illegible] isoprenaline are all potentially dangerous [illegible]ly in the postinfarction phase [illegible] arrhythmogenic and energy-consum[illegible] The lack of beneficial effect is also [illegible] reflexes due to the initial actions [illegible] been shown to increase myocardial [illegible] AMI but it also gives a marked chron[illegible] together with a decrease in peripheral [illegible] (2) Apart from these side-effects the [illegible] edly arrhythmogenic Dopamine [illegible] high doses increases heart rate and [illegible] sistance Both these drugs are ther[illegible] dangerous for the ischemic heart (4)

Dobutamine has been shown to exe[illegible] β 1 adrenergic stimulation resulting in [illegible] contractility with minimal positive [illegible] vasoconstrictive and arrhythmogenic [illegible] AMI patients the drug has been shown [illegible]

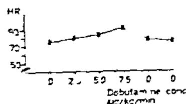


Fig 1 Heart rate in relation to concentration of dobutamine infusion (mean + S D) The increases at 5 0 and 7.5 µg/min are significant

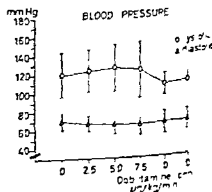
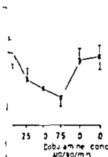


Fig 2 Systolic and distolic BP d[illegible] different [illegible]trations of dobutamine infusion (mean + S D) [illegible]nificant changes were noted



Relation between PEPI and different concentra dobutamine infusion PEPI was significantly d by dobutamine

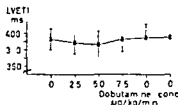


Fig 4 LVETI in relation to different concentrations of dobutamine LVETI was not changed by the drug

output and decrease pulmonary arterial pressures without significantly changing te or systemic arterial BP (8) This effect has n claimed to be non-demanding in energy l patients treated with dobutamine did not rger infarcts than control patients Further there was no increased frequency of pre VEBs (3) Four of our nine patients showed ase in ventricular ectopy during infusion reased frequency of VEB was concomitant e increase in heart rate An incidence of VEB is however not higher than expected in s with recent AMI (6) As pointed out by en et al (9) the action of dobutamine is ly energy-demanding as in patients with rately severe AMI the shortening of PEPI is ed with an increase in heart rate and BP ter AMI patients with more severe signs of failure in the above study did not respond ure pressure or PEPI but did show a signifi ncrease in heart rate These differences in re to dobutamine therapy depending on the e state remain unexplained Compensatory nisms especially in patients with severe con e heart failure may be relevant In these pa the sympathetic drive is nearly maximal and ther increase can be expected with a partly athomimetic drug like dobutamine our patients had "subclinical left heart fail d responded with a decrease in PEP and PEPI lso with a lowering of PEP/LVET suggesting sed contractility PEP measured according ssler and Garrard (10) has been shown to ate well with other parameters of contractility preload and afterload are held relatively con (5 7) In our study afterload—evaluated as or diastolic arterial pressures—did not change Preload or left ventricular filling pressures are shown to remain unchanged or decrease with the drug A decrease in preload is in itself associated with a prolongation of PEP (1) Accordingly there seems to have been an increase in contractility due to dobutamine The other two systolic time intervals used were PEP/LVET which is correlated to ejection fraction (11) and LVET which parallells stroke volume (12) Measured by these parameters ejection fraction increased whereas stroke volume was unchanged The increase in contractility is thus accompanied by the same decrease in diastolic as in systolic volumes The clinical value of this observation is limited as the reduction in PEP or PEPI is accompanied by an increase in heart rate suggesting further increases in oxygen demand This finding is discordant with original findings by Tuttle and Mills (8) in laboratory animals where the increase in contractility was not accompanied by increased heart rate The present data from patients with mild left heart failure after AMI do not suggest that dobutamine in this situation has significant advantages over isoprenaline dopamine or noradrenaline

Patients in shock accompanying myocardial infarction also fail to improve with dobutamine infusions (9) However dobutamine may well be of value during a limited period in patients with forward failure due to other conditions than ischemia i e septicemia postvalvulectomy where a reversible myocardial damage supposedly is present Results from the use of other β agonists are supporting this concept

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,tenolol Administered once Daily in Primary Hypertension

Effects on Blood Pressure in Relation to Pre Treatment Plasma Renin Activity

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Thomas Thulin and Kerstin Tolagen

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:T The antihypertensive effect of the selec ,drenoceptor blocking agent atenolol given '100 and 200 mg once daily, was evaluated ,nts with primary hypertension The drug ı efficient reduction of BP and in the whole ,es there was no difference in BP on either ,xercise tests performed in 10 patients, ,e same degree of partial β-blockade 24 r intake of 100 and 200 mg atenolol PRA during treatment with atenolol but there ,rrelation between the stimulated pretreat n level and the antihypertensive effect of Side-effects were few and 35 out of 37 ,ontinued on atenolol treatment Central de-effects were not seen

hypertension atenolol plasma renin activity
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,udies have shown a good antihypertensive the selective β 1 adrenoceptor blocking ,olol (Tenormin® ICI) (1 6 10) and long ,ies have revealed very few side-effects ,fficient reduction of blood pressure (BP) ,een achieved when atenolol has been ad l only once daily (4 7 23 28) thus pos ,easing patient compliance (12) Most β ,tor blocking agents depress plasma renin ,it has been suggested that this is one of ,s of action of the antihypertensive effect ,ers (2 3) It has also been proposed that ,pertensive response to propranolol can ,ted by determining the pretreatment ,nin activity (PRA) (2 27) which would a more individualized antihypertensive (16 21)

,m of this study was to evaluate the ,tensive and β blocking effect at rest and during exercise of atenolol administered once daily and to study the value of pretreatment renin profiling as a predictor of the antihypertensive response in patients with mild to moderate primary (essential) hypertension

PATIENTS AND METHODS

Thirty seven patients with primary hypertension participated in the study at three hypertension units Secondary forms of hypertension were excluded by clinical examinations and laboratory investigations as described earlier (19) Twenty six patients had not been treated earlier and antihypertensive therapy had been withdrawn in 11 for at least one month before this study

Patients with a supine BP ≥160/95 mmHg after a 4-week placebo period were randomized into two groups (A and B) for treatment (Table I) Treatment periods for group A were 4 weeks on 100 mg atenolol and then 4 weeks on 200 mg both doses administered once daily in group B the 200 mg period preceded the 100 mg period (Fig 1) The patients had taken their tablets about 26 hours before the last visit after 8 weeks on treatment All visits took place at the same time in the morning (8–10 a m) BP was measured in a quiet room after 10 min rest in the supine position and after 2 min in the standing position A mercury manometer was used and the diastolic pressure was registered when the Korotkoff sounds disappeared (fifth phase) All investigations at each center were performed by a highly trained nurse Heart rate (HR) was estimated by calculating the radial pulse for 30 sec

Ten patients were examined with dynamic work on a bicycle ergometer after 4 weeks treatment with placebo 100 and 200 mg atenolol All exercise tests were performed 24 hours after intake of tablets The initial exercise load was 50 W and increased stepwise by 50 W every 4th min until subjective maximal capacity Pulse and BP were registered after 2 and 4 min on each load The exercise was performed in the same way after each treatm period

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Abbreviations BP=blood pressure PRA activity HR=heart rate MAP=mean arterial LRH=low renin hypertension

Table I *Clinical data on the patients*

	Group A (n=19)	Group B (n=18)
Females	10	7
Males	9	11
Age (y)		
Mean	45	[illegible]
Range	26–64	32–65
WHO I	16	17
WHO II	1	1
Earlier untreated	12	14

Before entering the study patients were classified regarding their PRA profile according to a PRA frusemide test described previously (18). During treatment, blood was drawn for analysis of upright PRA at times indicated in the design of the study.

Paired Student's *t* test and conventional regression analysis were applied in the statistical calculations.

RESULTS

In both groups treatment with 100 and 200 mg atenolol once daily reduced BP in both supine and standing positions ($p<0.001$) compared to placebo for all except systolic BP on 200 mg in group B $p<0.01$) (Figs 2 and 3). In group A treatment with 200 mg reduced BP slightly more than treatment with 100 mg (supine $p<0.05$, standing $p<0.01$). No differences were noticed between BPs during the two regimens in group B.

There was a small difference in the number of responders (decrease in mean arterial pressure [M]AP) ≥10% compared to placebo) between pa[tient]s receiving 100 mg or 200 mg atenolol once [dai]ly (Table II). However the decrease in BP in the whole patient series (groups A+B) shows no dif-

Table II *Number of responders (de[crease in M]AP ≥10%)*

	Supine BP		Standing BP	
	100 mg	200 mg	100 mg	2[00 mg]
Group A	13	18	13	[illegible]
Group B	10	11	10	[illegible]

ferences between the final BP on 100 mg [and 200 mg] atenolol either supine or standing (dec[rease] and 18/15 mmHg respectively).

Treatment with 100 and 200 mg atenolol [reduced] HR in both groups (Figs 2 and 3). [HR was] reduced more ($p<0.05$) in group A at the [last] visit (200 mg dose taken about 26 h earlier) [than at] the preceding 4-week visit (100 mg atenolol [taken] the same morning).

The effects of atenolol given once daily [on MAP] and HR during rest and submaximal dynamic [exer]cise at 4 min 145 W are shown in Tab[le III and] Figs 4 and 5. At rest there was a signific[ant de]crease in MAP on both doses ($p<0.05$ ... exercise MAP was 14 mm lower on both d[oses than] on placebo but these differences were not [statisti]cally significant. The decrease in HR on both [doses] was significant both at rest ($p<0.01$) and [during] exercise ($p<0.001$).

Treatment with atenolol once daily decrea[sed up]right PRA significantly (Table IV) except [in pa]tients in group B on 100 mg when tablets w[ere taken] 26 h before the visit. There were no sig[nificant] correlations between the antihypertensive [effect of] atenolol and the initial stimulated PRA le[vel ...] eight patients with low renin hypertensi[on ...]

Table III *MAP and HR in 10 patients at r[est and] during 4 min exercise on 145 W (X±SD)*

	Placebo	Atenolol 100 mg	Atenolol 200 mg
At rest			
MAP (mmHg)	118±12	[illegible]	[illegible]
HR (beats/min)	79±14	61±[illegible]	[illegible]
During exercise			
MAP (mmHg)	142±18	125±15	[illegible]
HR (beats/min)	[illegible]±12	12[illegible]±9***	[illegible]

*$p<0.05$ **$p<0.01$ ***$p<0.001$ compared to placebo

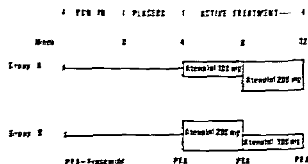
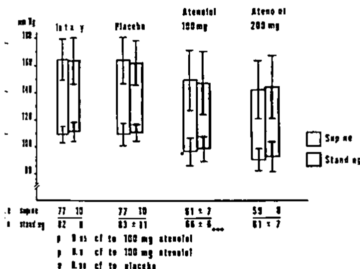


Fig 1 Design of the study

A ta [illegible] and 26



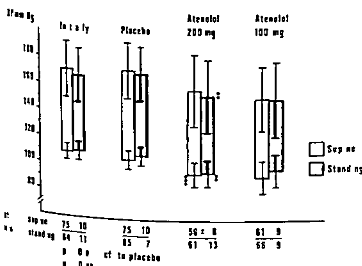
F g 2 Group A Sup ne and stand ng BP and HR (X + S D)

frusem de stimulated PRA <0 38 pkat 1 0 0 the decrease in MAP was only 10 compared to 16 mmHg in the e ght patients he h ghest ren n values (mean PRA 1 87 but th s d fference d d not reach statis gn f cance

effects were few 34 pat ents had no com Two pa ents reported cold extrem ties but them mpro ed after dose reduction from 200 100 mg atenolol once da ly One patient ex ced we ght gain anorex a and dyspnoea and ol had to be w thdrawn after 4 weeks of ent in a dose of 200 mg once da ly Th s had LRH by our def n t on

DISCUSSION

The present study clearly shows an ant hyperten sive and pulse reduc ng effect of the select ve β adrenoceptor block ng drug atenolol even when given as a s ngle da ly dose to pat ents with uncom pl cated primary hypertens on Clin cally relevant BP reduct ons were achieved w th both 100 and 200 mg given once da ly In group A 200 mg atenolol decreased BP slightly more than 100 mg but the patients had been on treatment for a longer t me (8 weeks) than on only 100 mg (4 weeks) In group B where the in tial da ly atenolol dose was 200 mg the decre se in BP was equally good when the dose after 4 weeks treatment was reduced to 100 mg



F g 3 G oup B Sup ne and stand ng BP and HR (X + S D)

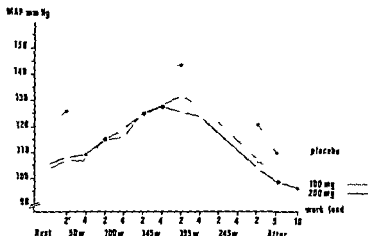


Fig 4 MAP at rest and during e
($n=10$)

We have previously investigated dose–response relationships for atenolol given in doses of 100–400 mg daily (10) According to that study 200 mg a day seemed to be optimal The present study shows that even 100 mg atenolol daily would be sufficient in most patients to reduce BP effectively which is in accordance with other reports (4 23 26)

Recent treatment policy with β adrenoceptor blocking drugs in hypertension has focused on giving the active agent only once daily and thereby possibly increasing patient compliance (8 17 25) The present study was designed to explore if atenolol could be administered as a single dose in the morning The results show that this is possible Despite a pasma half life of 6–9 hours (5) the antihypertensive and pulse reducing effects were prolonged and seemed to be sustained for at least 24 hours both at rest and during exercise

As the exercise tests shows 100 mg atenolol was icient to give a partial β adrenoceptor blocking effect throughout 24 hours or more and the dose (200 mg) did not result in a higher de β blockade This is in agreement with other (13 14 24)

Another observation indicating symp nervous inhibition is the effect on the PRA during treatment (Table IV) The PRA le upright position reflects the degree of sym stimulation As shown in Table IV patie received only 100 mg atenolol 26 hours befo was measured, exhibited no significant supp of PRA In contrast PRA suppression was demonstrated in patients in group A who ha 200 mg about 26 hours before the PRA sam drawn and also in both groups when PR measured about 2–4 hours after tablet inta may indicate that there are different mech for the suppression of renin and the decreas during treatment with atenolol

It would be an advantage in our cli

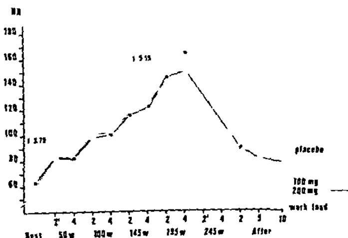


Fig 5 Mean HR (beats/min) at r during exercise ($n=10$)

PRA (plat l) before and d r ıı, tre t ıeı t ıth ater l l (X ± S E M)

In al y		Post frusem de	Placebo upright	Atenolol upright	
Sup ne	Upright			100 mg	200 mg
0 36 0 08	0 64 +0 12	0 68 +0 13	0 49 +0 13	0 ??* +0 08	0 13** +0 04
0 39 0 08	0 64 +0 11	1 05 +0 30	0 76 +0 ?1	0 ?7 +0 08	0 23* +0 06

**p<0 01 compared to upright pretreatment values

tens ve treatment ıf there was some sım ıem cal marker to pred ct the treatment to various ant hypertensıve drugs One hem al parameter has been proposed to and many authors have suggested that ıth normal to h gh PRA levels should be ter to β adrenoceptor blocking agents Moreo er ıt has previously been shown ocking drugs are almost ıneffectıve ın pa th LRH (16) Therefore we tested thıs us ın the present study Although the de BP was less ın e ght patients with LRH ents w h normal to h gh PRA the d f were not stat st cally signıf cant and there s gnıf cant correlat ons between pretreat ght PRA and the response to treatment d f om the decl ne ın MAP) Thus renın d d not p ed ct the response to antı sive treatment n the present study ecause the number of pat ents with LRH ted Another poss b l ty ıs that the pred c er of upright or frusem de st mulated PRA ak to be cl n cally relevant because many ctors are nvolved n the ma ntenance of n prımary hypertension (9) There was no r b ochem cal ev dence that patients with h gher PRA levels d ffered ın the r sodıum sium balance and there was no d fference ın electrolyte ex re on before treatment be te two groups

l n cal usefulness of a new ant hypertensıve y mu h d ctated by ts tolerance and of s de-effects In our study atenolol was d excellently and the s de effects were ın ry few The only relevant compla nts were to a decrease ın peripheral blood flow as ted by cold extrem t es n two pat ents and an ncrease ın exp ratory resistance with ospa m n ore pat ent

Central nervous s de effects have been described ın patients treated with non selective β blocking drugs (?9) We d d not notice any such effects and this agrees with a recent report demonstrat ng much less central nervo ıs side effects when pa tients were switched from propranolol to atenolol therapy (15)

We conclude that atenolol given once daily can be used as a safe and effic ent ant hypertens ve drug with a low frequency of s de effects A dose of 100 mg atenolol seems to be suff cıent n most patients to ınduce reduct on of BP and β blockade for ?4 hours

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...no Acid Metabolism in Patients with a Hereditary Myopathy and Paroxysmal Myoglobinuria

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...CT Amino acid metabolism of skeletal ...as examined in two patients with a hered... ...opathy associated with elevated blood lactate and pyruvate and paroxysmal ...uria Arterial concentrations as well as ...e exchange respectively of amino acids ...ruvate and oxygen were studied at rest and ...ercise (16 and 33 W) using a bicycle ergome... ...patients arterial concentrations of amino ...tate and pyruvate in the resting state were ... those of healthy controls During exercise a ...increase in lactate and pyruvate concentra... ...seen in the patients exceeding the small ...ealthy controls The arterial alanine concen... ...ose during exercise in both patients (+120% ...while no change was observed in the con... ...ing at the same work load No other amino ...wed a consistent rise during exercise In ...arterial levels of the branched chain amino ...ine leucine isoleucine) fell during exercise ...atients but not in the controls Net release of ...from the legs in patient 1 rose 2 5 and five ...ing exercise while no change was seen in the ... Alanine output from the working arms in ...2 exceeded that of controls by 50% In addi... release of lactate and pyruvate during exer... ...much augmented in both patients in com... ...to controls It is concluded that the rate of ...formation by skeletal muscle during exercise ...increased in patients with this type of myo... ...associated with elevated levels of lactate and ... These findings lend support to the theory ...e carbon skeletons for alanine synthesis by ... muscle are derived from muscle glycolysis

...ords alanine amino acid myopathy myoglo... muscle lactate pyruvate

...ed Scand 206 309 1979

...lobinuria is a known complication of McAr... ...syndrome a disorder characterized by lack of muscle phosphorylase (10) A less well recognized hereditary myopathy in which myoglobinuria also occurs (6) is associated with abnormalities in muscle glycolysis In response to mild exertion these patients show a much increased release of pyruvate and lactate from working muscle (7)

Studies in normal man have demonstrated that exercise stimulates the formation and release of alanine by muscle Release of alanine exceeds that of all other amino acids and is proportional to the circulating level of pyruvate (4) These and other observations have led to the formulation of the glucose–alanine cycle whereby alanine formation and release from muscle is determined at least in part by the availability of glucose derived pyruvate (3 4) In keeping with this relationship a diminished formation of alanine by muscle has been observed in patients with McArdle s syndrome in whom pyruvate availability is reduced (14) It is not known whether this relationship between pyruvate availability and alanine formation applies equally to circumstances of hyperpyruvicemia The present study was consequently undertaken to examine alanine metabolism in patients with a hereditary myopathy and hyperpyruvicemia as a means of further characterizing this disorder

SUBJECTS AND METHODS

Two patients with a hereditary myopathy associated with elevated blood levels of lactate and pyruvate and paroxysmal myoglobinuria were studied This disorder has previously been described in five families in Northern Sweden (6 7) The patients were siblings with healthy parents

Patient 1

A ?0-year-old non-obese female Since the age of 1? she had been easily fatigued even by light exertion and could walk only about 100 m on flat ground Her symptoms progressed with the addition of palpitations dyspnea and

Table I *Circulatory and hemodynamic data at rest and during leg exercise for patient 1*

	Rest	Exercise 16 W	33 W
Pulmonary oxygen uptake (ml/min STPD)	240	484	637
Expiratory exchange ratio	0 81	1 33	1 39
Heart rate (beats/min)	70	150	181
Arterial oxygen content (ml/l)	167 8	184 2	188 7
A-FV[a] oxygen difference (ml/l)	44 8	42 2	29 4
Hematocrit	40	44	45
Estimated leg blood flow (l/min)	0 65	6 4	14 5

[a] Arterial femoral venous

muscle pain after exercise at times with vomiting after heavier exercise The symptoms became progressively more marked and she had periods of pain in the back and shoulder muscles even in the resting state Dark urine was observed but myoglobinuria was not definitely established

She was hospitalized (University Hospital Umeå Sweden) at the age of 18 and showed a low physical working capacity (heart rate 170 beats/min at a bicycle work load of 30 W) as well as high pyruvate (0 24–0 35 mmol/l) and lactate (2 2–4 3 mmol/l) concentrations in arterial blood The maximum voluntary isometric force of several muscle groups including the leg [illegible] normal

A few months later she suffered an acute [illegible] with generalized muscle pain vomiting dys[illegible] cessive fatigue On re admission to the hosp[illegible] metabolic acidosis and high blood concen[illegible] lactate pyruvate and transaminases Myoglo[illegible] not observed These symptoms gradually [illegible] period of 4–6 weeks and left no marked seque[illegible]

At the time of the present study she still s[illegible] easy fatiguability and muscle pain upon exerc[illegible] fore her physical working capacity was low a[illegible] of only 30 W resulting in a heart rate of 170 beat[illegible]

Patient 2

A 22 year-old non-obese male who had always [illegible] physically fit than his classmates During [illegible] at 20 years of age muscle pain and fatigue prev[illegible] from participating fully in activities involving [illegible] exercise *His condition deteriorated gradually* [illegible] appearance of muscle pain in the resting state [illegible] ing muscle strength Red urine was observed [illegible] occasions He was hospitalized with generalized [illegible] pain and weakness and gradually developed pa[illegible] leg muscles subsequently extending to the [illegible] muscles and other muscle groups He required [illegible] treatment and electroconversion for ventricul[illegible] cardia and fibrillation Myoglobinuria was doc[illegible] After this episode he gradually recovered mus[illegible] but had persisting paresis and atrophy of the [illegible] muscle of both legs and became bound to a whee[illegible]

At the age of 22 he was examined at the [illegible]

Table II *Arterial concentrations and leg exchange of amino acids (μmol/l and μmol/min) a[illegible] and lactate (mmol/l and mmol/min) at rest and during leg exercise in patient 1 (P) and healthy co[illegible] (mean±S E M)*

	Arterial concentration						Leg exchange		
			Exercise						Exerc[illegible]
	Rest		16 W		33 W		Rest		16 W
	P	C	P	C	P	C	P	C	P
Taurine	25	37± 4	24	31± 3	26	31± 3	0	0±0	-4
Threonine	60	116± 5	53	93±11	52	93± 9	−1	−3±1	4
Serine	64	124±15	54	91±10	51	94±11	2	4±1	71
Proline	146	218±27	144	201±23	142	201±20	8	−5±3	29
Glycine	206	211±19	198	163±13	202	162±13	−9	−2±1	-11
Alanine	238	187±15	404	172±16	531	171±14	−26	−16±4	-64
α Aminobutyrate	13	30± 6	12	23± 5	10	23± 4	0	0±1	4
Valine	*260*	*234±26*	*242*	*186±20*	*233*	*183±17*	5	2±2	4
Cystine	87	110±11	85	75± 6	80	76± 9	1	6±2	7
Methionine	17	18± 2	21	16± 2	17	17± 1	−3	−1±1	7
Isoleucine	93	66±10	88	54± 7	77	54± 6	1	−1±1	11
Leucine	151	123±15	136	99±12	121	100±10	2	−1±1	71
Tyrosine	48	46± 5	49	38± 5	46	37± 4	−1	−1±1	-4
Phenylalanine	52	46± 4	48	38± 3	51	45± 9	0	−1±1	-4
Pyruvate	0 133	0 059±0 006	0 665	0 062±0 005	0 890	0 067±0 078	−0 001	−0 002±0 001	-0 [illegible]
Lactate	1 00	0 76±0 11	7 27	0 91±0 19	11 47	0 94±0 20	−0 08	0 03±0 02	-3 1[illegible]

Lmed Exercise tests on a bicycle ergometer arms (cranking) showed a high heart rate already work loads (33 W) and high concentrations of 2 mmol/l) and pyruvate (0 46 mmol/l) in arterial

d data for patient 1 were obtained from the study et al (14) Three healthy non obese volunteers d arm exercise and served as controls for patient patients and all controls were informed of the purpose and possible risks involved in the study giving their consent to participate

ects were examined in the postabsorptive state at e supine position and during upright exercise on a rgometer working with the legs (pat 1) and with (pat 2) Teflon catheters were introduced eously into the brachial or femoral artery and into ral or axillary vein The tip of the femoral venous was placed close to the inguinal ligament and that xillary venous catheter just outside the thoracic ng fluoroscopic control

tients exercised for 7–8 min at work loads of 16 Blood samples for analysis of oxygen lactate and amino acid concentrations were drawn at at each work load during exercise In addition te and pulmonary oxygen uptake were determined nd during exercise

nary oxygen uptake was measured using a bag and the Scholander micro-technique Heart as determined from the ECG Leg blood flow was ted from the pulmonary oxygen uptake and the

C
2±1
−2±1
0±4
2±7
−6±4
−23±4
0±1
11±4
7±3
1±1
5±1
8±3
2±1
2±1
0 011±0 003
0 19±0 05

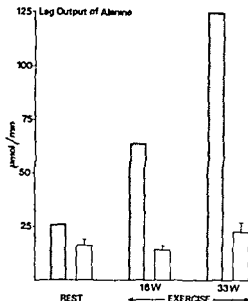


Fig 1 Leg output of alanine in patient 1 (▨) and controls (□) in the resting state and during bicycle exercise at 16 W and 33 W (mean ± S E M)

arterial femoral venous (A–FV) oxygen difference according to the formulas given by Jorfeldt and Wahren (5) Blood flow to the exercising arms was calculated on the assumption that 80% of the increment in oxygen uptake during exercise is utilized by the working arm muscles Arm blood flow at rest was assumed to be 0 5 l/min The methods employed for the determinations of lactate pyruvate individual plasma amino acids and hemoglobin concentration as well as oxygen saturation and hematocrit have been described previously (4 7 13)

All data in the text tables and figure are given as mean ±S E M

RESULTS

Patient 1

In the resting state patient 1 showed a normal pulmonary oxygen uptake and heart rate (Table I) The A–FV oxygen difference was slightly decreased and the estimated leg blood flow was approximately 40% greater than reported for healthy subjects (5) In response to exercise the pulmonary oxygen uptake rose in a normal manner in relation to the work but the rise in heart rate was much increased The estimated leg blood flow rose 10-fold above basal during exercise at only 16 W and increased more than 20-fold at 33 W

The arterial concentrations and the leg exchange of amino acids lactate and pyruvate in the patient and healthy controls are given in Table II The

Table III *Circulatory and hemodynamic data at rest and during arm exercise for patient 2 and control subjects*

	Patient 2			Controls					
		Exercise		Rest		Exercise 33 W		Exercise [illegible]	
	Rest	16 W	33 W	Mean	Range	Mean	Range	Mean	Ra[illegible]
Pulmonary oxygen uptake (ml/min)	285	696	1 106	280	260–292	877	804–964	2 100	[illegible]
Expiratory exchange ratio	0 74		1 11	0 83	0 77–0 88	0 88	0 79–0 96	1 04	[illegible]
Heart rate (beats/min)	60	163	196	56	52–69	82	74–90	166	[illegible]
Arterial oxygen content (ml/min)	202	215	227	178	171–185	180	176–185	190	[illegible]
A–AV oxygen difference (ml/min)	51 1	66 9	73 9	64	52–73	126	122–131	131	[illegible]
Arterial pH	7 41	7 37	7 30	7 41	7 36–7 47	–	–	7 33	[illegible]
Estimated arm blood flow (l/min)	0 5	4 9	8 9	0 5		3 8		13 0	

arterial levels in the basal state were all within the normal range (4 7) During exercise the patient s arterial concentration of lactate and pyruvate rose sharply Arterial alanine was the only amino acid for which a marked increase was observed During work at 16 W the alanine concentration rose to approximately 70% and at 33 W to as much as 125% above basal whereas for healthy controls exercising at an identical work load no rise was detected (Table II) No other amino acid showed a consistent rise in arterial concentration during exercise Instead the arterial level of several others notably the branched chain amino acids valine isoleucine and leucine fell during work and positive A FV differences were seen indicating net leg uptake of these amino acids

The net exchange of substrates for th[illegible] estimated from the product of leg blood [illegible] the A–FV differences The leg output of [illegible] patient 1 and controls is shown in Fig 1 [illegible] basal state the patient s output exceeded [illegible] controls by 60% This difference beca[illegible] greater during exercise the leg output of [illegible] rose 2 5 and 5 fold during work at 16 a[illegible] respectively whereas no significant ch[illegible] the basal level was seen in the controls exe[illegible] equal work loads In the patient a net upta[illegible] leg tissues of the amino acids proline [illegible] isoleucine and leucine was noted during [illegible] (Table II) Lactate and pyruvate output from [illegible] rose sharply in the patient in response to [illegible] cise (Table II) In contrast the healthy [illegible]

Table IV *Arterial concentrations of alanine pyruvate and lactate in patient 2 (P) and the controls (C) at rest and during arm exercise (mean and range)*

		Exercise		
	Rest	16 W	33 W	108 W
Alanine (μmol/l)				
P	170	262	374	
C	215 (206–223)		301 (288–313)	441 (381–500)
Pyruvate (mmol/l)				
P	0 10	0 34	0 47	
C	0 11 (0 10–0 11)		0 16 (0 14–0 18)	0 31 (0 28–0.34)
Lactate (mmol/l)				
P	0 80	4 60	9 15	
C	0 66 (0 61–0 73)		1 49 (1 27–1 91)	8 55 (5 9–11 8)

only a small output of lactate and pyruvate working legs at this light work load The te output observed in the patient was even han the value reported for healthy subjects ial work loads (4 0±0 8 mmol/min) (15)

y increased pulmonary oxygen uptake and l heart rate were found in the resting state II) During arm exercise at 16 and 33 W iptake and heart rate both rose sharply the ching 196 beats/min during exercise at 33 estimated arm blood flow in patient 2 was r increased during exercise and exceeded that of the controls working at an equal d

terial concentrations of alanine lactate vate in patient 2 were within normal ranges sal state (Table IV) In response to arm however the patient s arterial levels of ate and pyruvate rose substantially more ie controls and quite out of proportion to load (7) In the patient the arterial level of ose approximately 120% above the basal ing exercise at 33 W the corresponding the controls being 40% Alanine output exercising arms (33 W) in patient 2 was l at 120 µmol/min which exceeded the id n_6 value for the controls (78+10) by 150% Only during exercise at 108 W did y controls reach arterial concentrations of pyruvate and lactate comparable to those ie patient during work at 33 W No amino t from alanine showed a rise in arterial tion or a net release during exercise in instead the concentrations of threonine aline cystine isoleucine leucine and ll tended to fall

DISCUSSION

ges in arterial concentration and net re anine from muscle during exercise in the tients differ distinctly from those for the ntrols The rise in arterial alanine con in both patients was more marked than in the healthy subjects at similar work observed differences are far greater than ical errors involved in the determination concentration Moreover the estimated alanine from the working leg and arm respectively indicates that exercise induced hyperalaninemia in these patients is the result of a markedly augmented formation and release of alanine from working muscle (Fig 1)

With regard to the mechanism of alanine formation it is noteworthy that the patients developed a marked hyperpyruvicemia and showed an augmented release of both pyruvate and lactate from muscle during exercise Although measurements of intramuscular pyruvate concentrations were not feasible in this study the present findings suggest that the intracellular availability of pyruvate was much increased during exercise The augmented release of alanine from muscle and the elevated arterial concentrations of alanine during exercise in these patients thus lend strong support to the existence of a glucose–alanine cycle as suggested previously whereby alanine formation in muscle is determined in part by glucose derived pyruvate availability (3 4 14) Recent studies with the rat diaphragm have further supported the theory that the carbon skeletons for alanine formation by muscle are derived from muscle glycolysis (2)

As to the source of amino groups for alanine synthesis the branched chain amino acids (valine leucine and isoleucine) which are catabolized primarily in muscle (8 9) have been postulated to provide the nitrogen source for alanine formation in muscle (1 4) This has recently received experimental support from studies demonstrating that the addition of branched chain amino acids increases alanine formation by the isolated rat diaphragm (2 11 12) In agreement with this the augmented alanine production by our patients was accompanied by a fall in the arterial levels of valine leucine and isoleucine This phenomenon which was not observed in the healthy controls suggests that in the patients branched chain amino acids were taken up and degraded by working muscle thereby providing amino groups for transamination of pyruvate to alanine

The transamination of branched chain amino acids in muscle involves the formation of α ketoacids These may subsequently undergo oxidation thereby yielding 32–43 mol ATP per mol amino acid (11) Besides contributing to alanine production branched chain amino acid catabolism may thus be a significant source of energy for muscle in this disorder While the primary biochemical defect in the present type of myopathy remains to be established the current findings indicate that

increased formation and accumulation of alanine accompany the elevations in arterial lactate and pyruvate concentrations Thus it may be postulated that increased formation of alanine in these patients reflects a compensatory mechanism whereby accelerated catabolism of branched chain amino acids provides an alternative energy yielding process

During the light exercise employed in the present study, both of the patients developed disproportionate tachycardia hyperkinetic circulation and hyperventilation as well as symptoms of fatigue palpitations and local pain in the working muscles All of these findings reflect other aspects of this disorder and are in good agreement with previous reports (7)

ACKNOWLEDGEMENTS

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Pernicious Anaemia as a Risk Factor in Gastric Cancer

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ACT In order to assess the risk of gastric (GC) developing in patients with pernicious a (PA) the prevalence of PA was analysed in ents with GC notified to the Danish Cancer y in 1972 Among 877 patients with GC, PA eviously been diagnosed in 19 (2 2%) In seven PA had been diagnosed only shortly before ccordingly the diagnosis of PA could be re as unquestionable only in the remaining 12 1.3%) In either case the frequency of PA was antly higher than in a reference group of pa with cancer of the colon who had been selected same way Calculation of the incidence of GC patients showed that this was about three times than in the general population The annual GC was calculated to be 0 3% In PA patients mour was primarily localized to the body and of the stomach whereas it mainly involved the and pyloric region in patients without PA In f the low cancer rate it is concluded that e gastroscopy and barium meal examination indicated in PA patients in general Whenever nt with PA complains of dyspepsia, examina ith gastroscopy and barium meal should how e carried out on liberal indications

ords cancer risk gastric cancer pernicious a

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evalence of pernicious anaemia (PA) in Den has been found to be 1 3/1000 (1 7/1000 in 0 8/1000 in men) (9) From these figures it en estimated that in the country as a whole re about 6000 patients with PA Patients with e an excess risk of developing gastric cancer 3 8) It is generally estimated that the risk is three times as high as in the general popula) but the incidence of GC among PA patients from report to report in the literature (2) tly Gregor et al (5) reported an incidence of of GC in a series of PA patients followed period of 15 years

A difficulty in studies of this kind is that relatively large series of patients with PA have to be followed over long periods in order to establish a reasonably reliable incidence Furthermore the overall morbidity from GC is falling in the western world in Denmark it has been reduced to almost one half within the last decade (7)

We have therefore chosen to study the prevalence of PA in a series of patients with GC This prevalence is compared with that of PA in control patients with cancer of the colon

PATIENTS AND METHODS

Based on a list of cases of GC notified to the Danish Cancer Registry in 1972 inquiries were sent to the Danish hospital departments where these patients had been treated To a total of 998 inquiries 898 replies (94%) were received with case records or discharge summaries However 21 of the patients had to be excluded because of uncertain diagnoses In the remaining 877 patients the diagnoses had been established by biopsies at operation in 60% by autopsy in 28% by gastroscopy and biopsy in 6% while the diagnoses were based exclusively on barium meal examinations in 4% and on other methods such as lymph node biopsy or bone marrow studies in 2%

The series consisted of 533 men and 344 women The tumour was localized to the prepyloric region in 59% to the body of the stomach in 30% whereas it involved the fundus in 11% only

The reference series was selected on the basis of a list of cases of cancer of the colon notified to the Danish Cancer Registry during 1970 It consisted of 1777 patients—902 men and 875 women—with verified cancer localized to the colon or rectum

The statistical analysis of the data is based on the χ^2 test

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Abbreviations GC=gastric cancer PA=pernicious anaemia

Table I *Age and sex distribution of patients with GC cancer of the colon and PA*

Age (y)	GC				PA + GC				Cancer of the colon				PA a... of the d...
	Women		Men		Women		Men		Women		Men		Wom...
	N	%	N	%	N	%	N	%	N	%	N	%	(N)
20–29	2	0 6	0		0		0		5	0 6	4	0 4	0
30–39	6	2	5	0 9	0		0		11	1	7	0 8	0
40–49	10	3	21	4	0		0		40	5	36	4	0
50–59	26	8	62	12	0		2	22	115	13	117	13	0
60–69	68	20	171	32	3	30	2	22	246	28	302	33	0
70–79	165	48	193	36	5	50	3	34	313	36	285	32	1
80–89	65	19	75	14	2	20	2	22	132	15	139	15	0
>90	2	0 6	6	1	0		0		13	1	12	1	0
Average	71		70		73		70		69		68		
Range	26–93		31–93		66–84		54–87		21–101		24–93		
Total (n)	344		533		10		9		875		902		1

RESULTS

It appears from Table I that the age distribution of patients with GC is skew showing no difference between men with GC and patients with cancer of the colon

In 19 patients (9 men and 10 women) PA had been diagnosed prior to GC In 11 of these patients bone marrow studies haematological examinations or determinations of the serum level of cobalamin had verified the diagnosis of PA In the other eight patients it was not possible to establish the criteria on which the diagnoses had been based mainly because they had been made elsewhere and much earlier than the diagnosis of GC The age distribution of these 19 patients duration of PA and sites of the gastric tumours are recorded in Table II In ... of the 18 autopsied patients the tumour was ...zed to the body and fundus of the stomach All patients had received parenteral vitamin B_{12} injections either of a depot preparation (Betolvex®) or hydroxocobalamin (Vibeden®)

The majority of patients with PA and GC were over 60 years (Table I) i e the age distribution of PA patients was also skew However the average ages in the four groups of patients compared were roughly the same

In the group of men aged 50–59 years two out of 62 (3 2%) with GC also had PA this incidence is higher than that of PA in the reference group (0 out of 117) Similarly the age groups 60–69 70–79 and 80–89 years showed an overrepresentation of PA among the GC patients compared with the reference groups In the total group with GC we found that PA (19 out of 877) occurred with a frequ... 2 2% (1 3–3 4% at the 95% confidence li... the reference group the frequency of PA (... 1 777) was 0 2% (0 0–0 5% at the 95% confi... limit) which corresponds to the expecte... quency of 0 13% in the general population (... frequency of PA in patients with GC is signific... higher than in the reference group (p<0 0... the general population For the country as a ... it can be calculated that in 1972 about 6000 pa... suffered from PA (9) Based on the obs... number of cases of PA and co-existing GC (... 19 it can be calculated that GC will occur i... ciation with PA with an incidence of approx... 3 2/1 000 patients with PA In a popula... patients more than one half (54%) will be ... als aged 70 years or more (9) In this age g... total of 12 patients had GC associated with PA ... the incidence was 3 7/1 000 patients with PA (... of 6 000×0 54) (1 9–6 5/1000 at the 95% c... dence limit) As the 5 year survival rate for p... with GC within this age group is very lo... incidence can be directly compared with the m... ity from GC within the same age group ... general population which has been es... 1 3/1 000 (1 2–1 4/1 000)

DISCUSSION

The purpose of this analysis was to assess the ... of GC developing in PA patients We chose ... analyse the prevalence of PA in a series of pa... with GC and found that 2 2% of them had PA ...

I *Patients with PA and co-existing GC distributed according to sex age duration of symptoms and the tumour*

Sex	Age (y)	Duration of symptoms (y)	Site of tumour
♀	84	10	No autopsy
♀	72	20	Greater curvature
♀	66	8	Greater curvature
♀	75	37	Linitis pl greater curvature + fundus
♀	78	10	Greater curvature
♀	84	1	Prepyloric
♀	7[illegible]	1	Prepyloric
♀	73	10	Greater curvature
♀	67	30	Greater curvature
♀	72	1	Prepyloric
♂	84	15	Greater curvature
♂	54	9	Greater curvature + fundus
♂	87	1	Greater curvature + fundus
♂	72	1	Prepyloric
♂	72	12	Greater curvature
♂	72	9	Greater curvature
♂	55	6	Greater curvature + fundus
♂	69	1	Prepyloric
♂	66	1	Prepyloric

is about 13 times higher than that observed in rence group in which the prevalence of PA f the same order as in the general population series are corrected for the possibility that of the patients may have had a megaloblastic ia secondary to GC (all patients in whom the on of PA was less than 5 years excluded) (II) the prevalence of PA in the GC group 4% i e eight times as high as that expected by rved in the reference group This over ertation of PA among GC patients gives evi that the risk of developing GC is significantly r among PA patients than in the general popu The annual cancer rate (19 out of 6000) is er low (0 3%) compared with results of studies in which the overall risk has been ted to be 2 3% (5)

ong patients without PA the tumour was ed to the antral and pyloric region in more ne half of the cases By contrast only one of the patients with PA had cancer involving tral region If in addition one excludes pa with a disease duration of less than 5 years in the diagnosis of PA was questionable the ir was localized to the body and fundic region cases but one This observation strongly ts the assumption that GC in all patients with is a pathogenesis differing from that of other cases of GC In this connection it has been emphasized that the atrophic gastritis which in PA patients always involves the fundus and to a vary ing extent the body and pyloric antrum of the stomach (3) may predispose to the development of GC (10 11 12) In PA extremely high gastrin con centrations are often present in the serum and gastric mucosa (1) As gastrin is a trophic hormone for the fundus of the stomach it is reasonable to assume that a casual relationship may exist between the high gastrin levels and GC in PA patients (4)

Even though the risk of cancer is significantly higher in PA patients than in the population in gen eral routine gastroscopy or barium meal examina tion cannot be recommended in these patients For each cancer disclosed it would be necessary to examine 300–600 patients which in addition to the drain on resources would give rise to considerable mental strain in the individual patient On the other hand as atrophic gastritis does not produce symp toms any patient with PA in whom dyspepsia oc curs should be subjected to gastroscopy and barium meal examination

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Relief of Pruritus as an Early Sign of Spinal Cord Compression in Hodgkin's Disease

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ACT In a patient with advanced Hodgkin s (HD) associated with generalized pruritus an ted relief of itching was found to be an early spinal cord compression Following irradiation extradural mass at the Th II level itching 1. Although the mechanisms bringing about a HD are unknown the relief and recurrence symptom in our patient are in line with a ral origin of pruritus in the disease Spon relief of pruritus in HD despite other signs of disease should prompt a neurological examina the early recognition and treatment of spinal compression in lymphoma are important to residual neurological disability

ds Hodgkin s disease pruritus spinal cord com

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s is a common systemic symptom in n s disease (HD) and will disappear with ful treatment (3) We have observed a pa th severe pruritus associated with advanced whom clinical signs of progressive disease nexpectedly accompanied by a reduction of s The relief of itching turned out to be an sign of spinal cord compression due to an ral manifestation of HD

CASE REPORT

ient is a 33-year-old man with the nodular sclerosis HD clinical stage IV diagnosed in 1972 Initial nt with the MOPP chemotherapeutic regimen was ful but since 1977 there have been progressive ms of HD de pite several attempts to control the with various schedules of chemotherapy Fever eat and a severe generalized pruritus have been for the last year A destruction in his sternum was n Oct. 1978 and at the same time a subcutaneous in the thoracic wall became palpable Fine needle aspiration biospies showed that the sternal and cutaneous lesions were caused by HD

In Jan 1979 pruritus in the trunk and lower ext emities improved remarkably However the subcutaneous lesion was unchanged and the patient had persistent fever night sweats and an elevated ESR 60 mm/h indicating persis tent active disease He also got pains between the shoulders and physical examination revealed an impaired sensibility for touch below the breast nipples There was no impairment of motor functions and the tendon reflexes were normal

Myelography revealed a spinal cord compression due to a left sided lateral extradural tumour at the Th II level and radiation therapy was instituted The pain between the shoulders disappeared after about 10 days Pruritus returned concurrently in the trunk and legs and generalized pruritus again became a troublesome symptom

DISCUSSION

The disappearance of pruritus in our patient was obviously not due to a proper control of his disease by chemotherapy On the contrary the persistent cutaneous lesion fever and elevated ESR indicated a considerable activity in his lymphoma The most probable explanation of the relief of pruritus is that the compression of the spinal cord affected the spino-thalamic tracts known to transmit the itching impulses (2) The finding of a coexistent hypoesthesia in the trunk and lower extremities is also compatible with an affection of the spino thalamic tracts Moreover the pruritus returned following decompression of the spinal cord by radiation treatment of the extramedullary tumour mass

The outcome of spinal cord compression in malignant lymphoma largely depends on the initial neurologic symptoms When there are minor neurologic deficits the chances of recovery following radiation therapy are good The results of treatment become poorer when more advanced

neurologic symptoms with motor dysfunctions are present (1) Early diagnosis and treatment of spinal cord compression in patients with HD are therefore of utmost importance (3) In patients with signs of progressive disease and with systemic symptoms like fever and pruritus a spontaneous relief of itching should evoke suspicion of spinal cord involvement and prompt a neurological examination

Although the mechanisms bringing about pruritus in HD are still unknown (4) the relief of pruritus associated with spinal cord compression and the recurrent symptoms following treatment point to a peripheral origin of itching in HD

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Isochromosome 17 in a Patient with a Myeloproliferative Disorder Terminating in Eosinophilic Leukemia

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the S on of Onc l g and Hen ol g tl e Dep rtme t f Med c ne Hudd nge Ho p tal H dd n e he In t te of Med cal Cell Genet cs K ol nska Inst te S ockl lm and the Department f Med c ne Esk l t na Hosp al Esk lst na Sweden

CT A pat ent is described who for more years had a myeloproliferative disorder minated in eos nophilic leukemia Chromo- l sis re ealed an isochromosome 17 in all es of bone marrow cells This abnormality been found in two out of six patients with c leukem a investigated by band ng tech nd may therefore have etiologic importance ome analys s in the hypereosinophilic has pract cal value for d fferentiating and non mal gnant d sease

eo noph l c leukem a isochromosome 17 cy

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w th eos noph l a n the per pheral blood l r on and heart damage w th no known for many years posed a d ff cult ques b s a mal gnant or a non mal gnant d s elberg (22) strongly doubted that eos no kemia ex sted Bentley et al (2) tried to spec fc criteria for the d agnosis wh le l Anderson (15) preferred to talk about the noph l c syndrome

osome analysis may help to resolve th s s nce the presence of a spec fic non-con chromosomal aberrat on in bone mar s generally accepted as a s gn of a pre o mal gnant cell clone Before band ng s were available chromosome analyses in cases of eos noph l c leukemia had re Philadelph a chromosome (Ph) n some ut n most cases no consistent abnormali und Only a few pat ents have been n l w h band ng techn que This report de pa ent w th a myeloprol ferative d sease wh ch terminated in a hypereos noph l c syn drome Using the Q banding technique a con sistent chromosomal abnormal ty was found in all bone marrow cells

PATIENT AND METHODS

P ent l st r

The pat ent was a wh te male born in 1906 who had been a foundry wo ker S nce 197? he had had symptoms and s gns thought to be caused by ischem c heart d sease and eas ly managed w th d uret cs and n troglycerin

In July 1975 at a rout ne out pat ent v s t because of the heart compla nt a h gh Hb level 170 g/l and an elevated *WBC 18 4×10⁹/l* were observed *Bone* marrow asp rat on showed a normal amount of fat thrombocytopo es s and myelopo es s were rather act ve and there was some eos noph l a The pat ent felt well there was no glandula hyperplas a no hepato- och splenomegaly nor has there been any s nce then *In Feb 1976* he was hosp tal zed in h s home town because of gastric bleed ng but felt oth erwise well unt l Sept 1977 H s Hb level was h gh unt l then as a rule around 190 g/l and WBC 12 2 16 9×10⁹/l Thrombocyte count was elevated w th a h ghest recorded *level of 131?×10⁹/l In Sept 1975 the d ff rent al count* showed 16% eos noph ls ncreas ng to 4 % one year later Basoph l c granulocytes were around 3% n those years Four consecut ve marrow asp rat ons showed less and less fat and more and mo e act ve proliferat on of all *cell l nes (Tables I and II) The red cell volume was h gh* plasma volume normal and there were no s gns of pulmo- nary d sease Polycythem a vera was strongly suspec ed and n Aug 1977 he rece ved 5 mC ³²P

In Sept 1977 the pat ent fell ll w th a cough and a h gh *sp k ng fever X ray showed extensive fast-chang ng* pulmonary inf ltrat ons No nfect ous or paras t c d sease could be diagnosed and h s illness abated on 80 mg p ed n solone da ly The pulmonary inf ltrat ons d sappeared The muscular b opsy unfortunately not performed befo e the pat ent had rece ved stero ds d d not show abnormal vessels The Hb level fell and he needed transfus ons keep t at 80–100 g/l Thrombocytes also fell to 100×10⁹/l They were of b zarre conf

Table I *Hematological laboratory data (peripheral blood)*

	Sept 1975	Nov 1975	March 1976	Dec 1976	Oct 1977	Nov 1977	Jan 1978
Hb (g/l)	190	190	132	190	95	92	89
Platelets ($\times 10^9$/l)	1 312	420	297	625	135	107	105
WBC ($\times 10^9$/l)	12 1	16 2	12 2	14 9	26 5	27 0	[illegible]
Eosinophils (%)	16	16	18	42	24	44	34

giant forms some were even larger than the eosinophilic granulocytes The WBC climbed to around 35×10^9/l with 20–25% mature eosinophils 6–7% basophils and 20–25% eosinophilic metamyelocytes and myelocytes Less than 2% blastic cells appeared inconsistently in the differential count The marrow displayed corresponding changes erythropoiesis and thrombopoiesis decreased the now massive cellularity was caused by increasing amounts of early eosinophilic cell forms which dominated the picture

In Feb 1978 the patient was admitted to Huddinge Hospital for further diagnostic studies Chromosome analysis was performed at this time (see below) The WBC on that day was $28\ 6\times10^9$/l with 55% eosinophilic granulocytes one third of them being metamyelocytes and myelocytes Platelet count was 171×10^9/l Hb 81 g/l Lysozyme in serum 12 6 μg/ml (normal 5–10) Vitamin B_1 in serum 1 140 pmol/l (normal 200–750) LAP index (patient score/control score$\times$100) 43 9 in blood 65 3 in marrow Total heart volume was 890 ml corresponding to 580 ml/m² BSA ECG showed sinus tachycardia and ST T changes corresponding to the posterior wall of the left ventricle ECG during exercise giving a pulse of 155/min showed no further changes Two weeks later the patient developed a fast atrial fibrillation Echocardiographic studies showed right ventricular hypertrophy confirmed by ²⁰¹thallium scintigram which also showed a defective uptake corresponding to the posterior wall of the left ventricle Angiographic studies of abdominal arteries did not show the characteristic microaneurysmatic changes sometimes seen in periarteritis nodosa

The disease was interpreted as
The patient was treated with busulfan for riod only due to lack of response and thrombocytopenia Prednisolone 90 cristine 2 mg weekly kept the fever and infiltrations under control

On March 9 1978 the patient de consistent with a cerebral thrombosis or hemorrhage and he died on March 21 1978 studies were not undertaken

Cytogenetic analysis

Metaphases from bone marrow ce ly from fresh aspirates Metaphases from cells were prepared after 72 h in c phytohemagglutinin Staining was perform to the Q banding technique (6) *Metaphases* and photographed in a fluorescence micr karyotypes were then prepared using conve nique

RESULTS

Twenty bone marrow metaphases were All had an isochromosome 17 (Fig 1) o extra chromosome no 13 No other abr were found Six peripheral blood meta also analysed All showed normal karyot

Table II *Bone marrow differential count (% cells)*

	July 1975	Nov 1975	March 1976	Oct 1977	Nov 1977	Jan 1978
Neutrophilic cells (granulocytes + meta myelocytes + myelocytes)	40	50	41	21 5*	71 5*	19*
Eosinophilic cells (granulocytes + myelocytes)	20	14	15 5	39 5	14 5	55
Promyelocytes	6	4 5	5 5	6 5	7 5	5
Myeloblasts	3	0 5	2	13	4	7
Red cell precursors	17	24	20 5	14 5	1	9
Other cell types	14	7	15 5	5	1 5	5

* Many pseudo-Pelger Huet cells and heavy toxic granulation

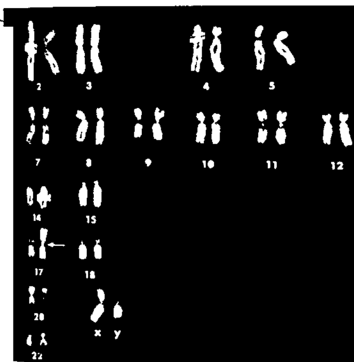


Fig 1 Karyotype from a bone marrow cell showing isochromosome 17 (×925)

DISCUSSION

t presented with a myeloproliferative kin to polycythemia vera The disease ssed and acquired all the criteria of the ophilic syndrome

l above the nature of the hypereosino- rome has been much debated Arguments ndrome including Loffler s endocarditis parietalis fibroplastica is malignant are the frequently very poor prognosis and the heavy organ infiltration of eosinophilic cells Many patients have other symptoms compatible with a premalignant or malignant myeloproliferative disorder such as erythrocytosis (16 24 26) myelofibrosis (3 14 23) high serum vitamin B_{12} level (8 11) high percentage of basophilic cells in the peripheral

Chromosome analysis (Q banding or G banding) in six patients with eosinophilic leukemia

Duration of disease (mo)	Myocardial involvement	Serum vitamin B_{12}	LAP score	WBC (×10^9/l)	Eosinophils (%)	No of abnormal metaphases/ total metaphases	Chromosomal abnormality	Ref
7	None	Normal	High	45 0	67	20/20	47XY +8	27
>[illegible]	None	High	Low	47 5	88	60/60	46XY isochromosome 17	21
6	Yes	Not reported	Not reported	300 0	80	31/37	47XY +10	13
3 5	Yes	Not reported	Low	33 0	65	42/43	49XYY t(3 5) +8 + marker	4
33	Yes	High	Low	22 6	55	Not reported	46XY short Y	10
33	Yes	High	Low	35 0	55	20/20	46XY isochromosome 17	Present study

blood (8 28) impaired eosinophilic maturation (5) and most important chromosomal aberrations in the bone marrow cells (5 8 27)

Before the banding technique became available Chusid et al (8) reported that 7 out of 13 investigated patients with the hypereosinophilic syndrome had abnormal karyotypes One of these patients had a Ph¹ in all bone marrow metaphases and another six Ph¹ positive patients have been described (27) A case with a double Ph¹ has been reported recently (1) However there does not seem to be any record of the typical t(9 22) translocation in eosinophilic leukemia Only 6 patients have so far been reported after investigation with banding techniques (Table III) Trisomy 8 trisomy 10 isochromosome 17 and a short Y chromosome are the abnormalities found It is interesting that all these abnormalities have also been found in chronic myelocytic leukemia (7 9 12 19) With the exception of the Philadelphia chromosome they are generally found only shortly before or during blastic transformation In rare cases trisomy 8 may also be found in a chronic stage of chronic myelocytic leukemia (18 19 20) These abnormalities may also occur in other myeloproliferative disorders (17) For example trisomy 8 is one of the most common aberrations in acute myeloblastic leukemia and is also found in polycythemia vera (25) Isochromosome 17 has also been demonstrated in other leukemias and lymphomas (4 18 25)

The spectrum of chromosomal abnormalities in patients with the hypereosinophilic syndrome clearly indicates that this disease includes a premalignant or malignant myeloproliferative disorder related to leukemia which could probably best be called eosinophilic leukemia Whether the chromosomal abnormalities have the same prognostic implications as in chronic myelocytic leukemia is however uncertain Although isochromosome 17 was found in our patient only about one month before death blast cells were not predominant Unfortunately chromosomal analysis was not carried out early in the disease and therefore it is not known whether the patient had the abnormality already at its onset 3 years before death In other patients (Table III) trisomy 8 trisomy 10 and isochromosome 17 were not reported to be associated with a rapid course of the disease This agrees with our previous impression that the specific chromosomal disorders do not have the same prognostic implications in different variants of the syndrome

ACKNOWLEDGEMENTS

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Acta Med Scand 206 327–332 1979

Isovolemic Hemodilution in Erythrocytosis Secondary to Chronic Obstructive Lung Disease

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ACT Patients with chronic obstructive lung often present with a combination of respiratory and circulatory insufficiency In secondary erythrocytosis (polycythemia) blood viscosity rises and further impairs peripheral oxygenation Against this background a patient with acute exacerbation of chronic respiratory disease with secondary erythrocytosis was treated with isovolemic hemodilution during two periods of hospitalization During each of these periods hemodilution was achieved by removing 1700 and 1750 ml blood, respectively and replacing this simultaneously by infusing equal volumes of dextran 70 (Macrodex®) The patient s general condition improved her dependence on supplementary oxygen drastically decreased and the blood gas values improved after hemodilution The course of the disease in this case suggests that the high hematocrit rather than hypervolemia contributed to the patient s poor condition It also illustrates that too intensive diuretic therapy in cardiac insufficiency with concomitant erythrocytosis can cause hemoconcentration and thereby add to the strain on an already overloaded circulation

Key words hemodilution lung diseases—obstructive polycythemia

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In respiratory insufficiency is a very serious condition for the patient exceptionally distressing conditions Conventional means of treatment seldom result in any marked improvement and in non in some cases respirator treatment is hardly practical In chronic obstructive lung disease with secondary erythrocytosis impaired central and peripheral circulation can contribute to impaired tissue oxygenation In such cases hemodilution can be a valuable supplement to conventional therapy

THE PATIENT AND METHODS

The patient was a 67 year-old woman with symptoms of chronic bronchitis for 20 years She used to be a heavy smoker but in recent years her cigarette consumption had been about 10 per day Breathing difficulties had increased over the last four years and the least exertion resulted in considerable breathlessness Since 1975 she had had oxygen at home and generally had to use it several times a day She had been admitted to the hospital on several occasions during the last 3 years because of acute exacerbation of breathing distress On these occasions blood gas analyses revealed hypoxemia hypercapnia and a compensated respiratory acidosis Spirometry showed considerably obstructed ventilation Blood tests showed erythrocytosis There was no deficiency of α_1 antitrypsin For many years the patient had been treated with β adrenergic receptor stimulators theophylline preparations expectorants and in certain periods corticosteroids and broad spectrum antibiotics In addition she has been on digitalis and diuretics for a long time

The description below refers to the progress of the disease during two periods of hospitalization (March and Oct 1977) when the patient s acute stages of respiratory and circulatory insufficiency were treated by isovolemic hemodilution On both occasions the patient was dyspnoic darkly cyanotic and in very poor general condition on admission There were no signs or symptoms of infection On the second hospitalization there was slight ankle edema slight dilatation of the pulmonary vessels detected by radiography but the size of the heart was within normal limits

During the first stay in hospital the patient was treated with breathing physiotherapy salbutamol 4 mg×4 proxiphyllin 0 4 mg×3 ACTH injections (max 60 IU×4) digitoxin tabs 0 1 mg×1 expectorant and when necessary proxiphyllin 0 1 g/ml 4 ml i v and adrenaline 1 mg/ml 0 5 ml s c In addition she received oxygen via nasal catheter to meet subjective requirements which initially meant almost continuous oxygen administration This therapy was administered for 6 days without any *change in her general condition In order to reduce the* pronounced tissue hypoxia hemodilution was initiated on the seventh day and carried out over a period of two weeks whereby a total of 1 700 ml venous blood (5×300–500 ml) was removed and immediately replaced by the same volume of dextran 70 (Macrodex®)

During the second hospitalization initial treatment was the same as during the first Two days after admission the patient received i v injections of furosemide (Lasix®) 40 mg 2×3 and proxiphyllin (Theon®) 4 ml×4 for four days because of increasing difficulty in breathing with signs of cardiac incompensation

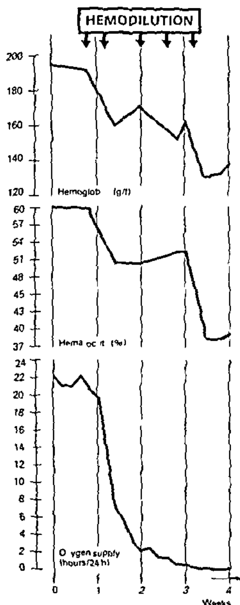


Fig 1 Effect of hemodilution on *Hb concentration Hct* and oxygen adm nistration during the first hospitalizat on

As the *patient s condition* successively deteriorated over the following weeks *isovolemic hemodilution* was again carr ed out This time a total of *1750 ml blood* was *removed* and simultaneously replaced by dextran 70 infu sions on five occas ons

RESULTS

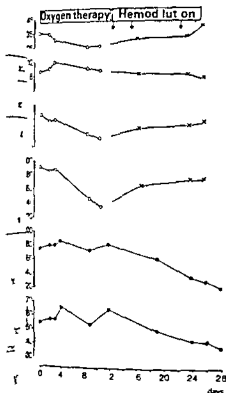
During the first stay in hospital the patient received *traditional* treatment for respiratory distress for six *days without* improvement After hemodilution Hb *and* Hct decreased the dependence on sup plementary oxygen diminished and the oxygen

Table I *Blood gas values* ... *plementary oxygen during the first* ... *period before and after hem d l t n*

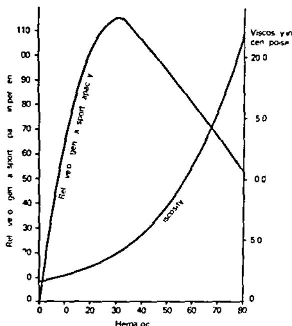
	Before	
	With out O_2	With O_2
aB – pH (U)	7 40	7 39
aB – CO_2 (kPa)	8 4	7 7
B – standard bicarbonate (mmol/l)	35	3[illegible]
aB – base excess (mmol/l)	+12	+8
aB – O_2 (kPa)	4 0	4
aB – O_2 saturat on (%)	60	68

administration could be successively re... I) In spite of this the blood gas values ... (Table I) Spirometry values were on ... h nd unchanged after hemodilution w th ... structed and restricted ventilation ... 1 6 l (3 0) residual volume 4 1 l (1 5) FE... (2 2) FEV 31% (70) MVV 15 l min (... lated normal values are given in paren hese...

During the first two weeks of the second ... stay conventional treatment of the res... cardiac insufficiency gave no improvement ... contrary the patient s condition con... teriorated with both clinical and rad logic ... toms of increasing cardiac insufficiency ... institution of hemodilution her general ... rapidly improved and the card ac ... regressed The patient s Hb concentration ... blood gases during the second stay in ... presented in Fig 2 It is important to n... samples for blood gas analyses taken ... period of oxygen therapy were drawn w... was being administered whereas s... during the hemodilution period were ... oxygen was not being administered The ... provement in blood gas values aft r hemodil... thus better than that presented in Fig ... evident from Fig 2 that Hb and H... rose at the beginning of hospita... hemoconcentration coincides with the ... diuretic therapy 240 mg furosemide ... which was prescribed in order to reduce ... incompensation Hct thus rose from ... imum of 67% The patient s blood gas ... cessively deteriorated at the beginning of ... zation and at worst pO was 3 9 kPa ...



lood gases Hb concentra on and Hct during ad hospitaliza ion O Oxygen was be ng ted when b ood gas samples were taken x = no ary oxygen was admin stered at the t me of



F g 3 Relat onsh p between Hct relat ve oxygen transport capac ty and blood v scos ty (Af er H nt (11))

gen saturat on was 33% desp te cont nu gen adm n strat on Blood gas values only l when sovolem c hemod lution was per A e dent from Fg 2 the Hb and Hct re mirro images of the pO_2 and O_2 satura es the most serious blood gas d stur occurring when Hct was h ghest Hct re o r rmal after hemod lut on wh le blood es approached normal Thus after both of hosp talizat on the patient could be d s in good cond on During the intervening th period she felt in better cond t on than in ious year except for the few weeks imme no to readm ss on

DISCUSSION

w th ch on c obstructive lung d sease often rom a comb nat on of resp ratory and ory in uffc ency The resp ratory insuff s mainly due to nsuffc ent alveolar vent lation in relat on to the product on of carbon d ox de and th s leads to chron c hypoxem a and hypercapnia (4) These chron c changes in the blood gases cause a number of hemodynamic dis turbances at both central and peripheral levels Thus in advanced cases an increase may occur in pulmonary vascular res stance pulmonary hypertension right chamber insuffc ency hyper volem a and secondary erythrocytos s w th ra sed blood v scos ty (16 20 23)

Hypervolem a commonly occurs in chron c ob struct ve lung disease (10) The importance of hypervolem a in the et ology of pulmonary hypertension is not yet clear Certa n authors con s der that hypervolem a is of l ttle or no mportance in th s situat on s nce no reduct on of pulmonary arterial pressure has been noted after the reduct on of blood volume (1 2) Gertz (8) however cons d ers that hypervolem a contributes to the development of pulmonary hypertens on and hypoxem a and therefore recommends long term treatment with d uret cs in order to ma ntain a normal blood volume

Pat ents with chron c obstruct ve lung d sease show much the same erythropo et c response to chron c hypox a as normal persons (23) The fact that man fest erythrocytos s is relatively unusual in

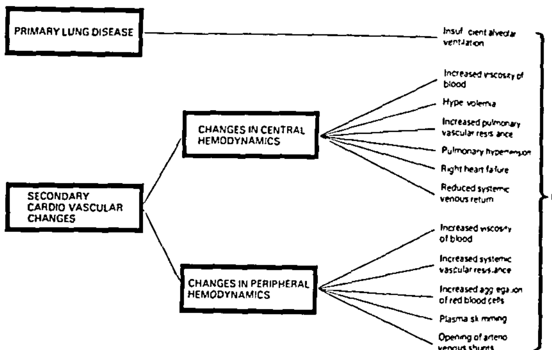


Fig 4 Schematic representation of factors contributing to hypoxia in chronic obstructive lung disease with secondary erythrocytosis

hypoxic lung disease has been ascribed to suppression of bone marrow by hypercapnia and to repeated airway infections (20) Also an increased plasma volume will give a normal Hct value in spite of secondary erythrocytosis (20) In acute exacerbations of respiratory insufficiency nutrient and fluid intake are often reduced and this can cause a hidden erythrocytosis to become overt

In secondary erythrocytosis with raised Hct the viscosity of blood is also raised which can lead to peripheral resistance reduced capillary flow reduced venous return and reduced ac output (13) In addition the viscosity of blood rises exponentially with rising Hct (Fig 3) (11) Karp et al (12) found that pulmonary vascular resistance increased proportionally with increasing Hct and considered viscosity to be an important factor in pulmonary vascular resistance Within the microcirculation erythrocytosis and hemoconcentration increase the tendency for red blood cells to aggregate which together with the raised viscosity leads to sluggish blood flow and impaired oxygen supply to the tissues (15) Plasma skimming and opening of arteriovenous shunts are other phenomena which occur in erythrocytosis and contribute to tissue hypoxia (7) Hypoxia thus has a multifactorial etiology in advanced chronic [...] tive lung disease and can be attributed partly [...] primary lung disease and partly to the se[...] central and peripheral hemodynamic c[...] (Fig 4)

Hemodilution (exchange transfusion) [...] utilized to break this vicious circle of [...] and circulatory disturbances Hemodil[...] that the blood is diluted by removing a cert[...] ume of blood and simultaneously infus[...] responding volume of an osmotically a[...] tion In order to maintain isovolemia in [...] tion colloid solutions such as dextran 40 [...] must be used (22) The reduction of H[...] hemodilution reduces blood viscosity and [...] eral resistance and increases venous re[...] cardiac output These effects result in incr[...] capillary perfusion and oxygen transport [...] the fact that hemodilution reduces the con[...] tion of oxygen bearing components (re[...] cells) increased peripheral oxygenation [...] achieved because of the improvement in cir[...] culation (11) For rheological reasons the c[...] transport capacity of blood is greatest at a [...] around 30% i e somewhat lower than normal [...] 3) This has been theoretically calc[...]

l confirmed by an mal experiments and
studies in man (14 15)

... of treat ne erythrocytos s is venesec
... e procedure however has not been shown
... long term effect on blood gases or
... hemod nam cs Only a short acting tran
... bjectı e effect has been observed (5 19)
... hemod lut on has been recommended
... tional reduct on of the red cell volume (18)
... ues can be dra t cally reduced by this
... Gregory (9) reported that up to 3500 ml
... ld be exchanged without injury to the
... He has performed hemod lut on with
... 40 n pat ents with erythrocytosis cor
... peripheral arterial insufficiency with
... ging re ults

... te cardiac insuff c ency and erythrocytos s
... ent s multaneously it should be borne in
... although d uret cs adm ttedly reduce plas
... me they leave the red cell volume un
... l Th s causes an already raised Hct to rise
... wh ch leads to a further increase in blood
... y and worsened per pheral circulat on with
... ted t ssue hypox a (17) Th s phenomenon
... ed in our pat ent during her second period
... l The fact that her condit on deteriorated
... tic therapy but improved after isovolem c
... on suggests that a ra sed red cell volume
... n a raised blood volume was respons ble
... rticular pat ent s poor condition

... 0 s excreted via the k dneys to a lesser
... n dextran 40 and remains longer in the
... on. S nce our primary intention was to
... the ra sed Hct we used dextran 70 (Mac
... which is a superior plasma expander in the
... m (7)

... m c hemod lut on in a patient with acute
... tory d tress because of chron c bronch tis
... econdary erythrocytos s has on two occa
... ersed an expected fatal outcome S nce
... w th severe chron c obstructive lung dis-
... e a prognos s comparable to that in
... ant d sease (3) one should util ze every pos
... for symptomatic improvement With this
... ication we w sh to po nt out the value of
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LETTERS TO THE EDITOR

PROPRANOLOL FOR THE EATMENT OF HYPERTENSION IN PREGNANCY

n hown that 40–60% of Brit sh obstetr c ans sonal e perience w th propranolol treatment of h perten on n pregnancy (1) A s m lar develop curs probab y n Scand nav a I f nd it mportant to ze that th s treatment s st ll controversial

anolol dec eases card ac output and increases al arterial res stance w th a resultant reduct on in ral c rcula on nclud ng probably the uterus and a The va oconstrictor effect must be cons dered preeclamp a, because vasoconstrict on is an es pathogen c feature n severe preeclamps a and ia. Mo eover propranolol crosses the placenta harm the foetus

reports have suggested a causal ty between olol reatment and placental insuff ciency sed foetal tachycard c response to hypox a re ry d pre s on at b rth and hypoglycaem a ardia and hype b l rub naem a during the neonatal There ha e been no reports of congenital malfor re a ed to propranolol

esen fou uncon rolled series of 20 10 76 and 9 e have been publ shed all ind cat ng no mater foetal complicat ons of propranolol treatment (2 Recently a series of 24 pregnanc es (propranolol nt 9 o her ant hypertens ve treatment 15) has in poore foetal prognos s assoc ated w th pro- ol treatment (4) The st mulat ng effect of pro- n on u erine tone does not seem to be a s gn f cant m in practical obs etrics

ano of trea ment s perhaps really harmless during ncy and compl ca ons may be rare but larger led pro pective nvest ga ons to conf rm th s are ey la k ng at present Consequently pro- ol hould not be used rout nely during pregnan d if u ed the treatment should be g ven with in ten on

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ELECTRICAL ALTERNANS

S r

We would l ke to comment on a recent case report o phas c voltage alternat on in spontaneous left s ded pneumothorax (1)

We have recently seen a s m lar case n a 51 year-old man who presented to our Out Pat ent Department Three weeks previously he had developed a sudden onset of left s ded chest pain assoc ated w th moderate dyspnoea Th s n t ally resolved but he cont nued to not ce occa sional left s ded chest pa n and m ld dyspnoea on exert on over the next three weeks Phys cal exam nat on revealed the s gns of a left sided pneumothorax and chest rad o- graph conf rmed th s w th the pneumothorax occupy ing approx mately 50% of the lung f eld

An ECG showed phasic voltage alternat on n several leads (F g 1) We would l ke to suggest that desp te the apparent lack of case reports in the wo ld l terature phas c voltage alternat on may occur more commonly than s recogn sed n left s ded pneumothorax Th s may not be detected for the s mple reason that ECGs are rarely performed in these pat ents

S m larly we would l ke to challenge the suggest on that the ECG is a useful d agnost c tool n the d agnos s of pneumothorax s nce electr cal alternans may occur in per card al effus on (?) Pneumothorax surely rema ns the impenetrable doma n of the chest rad ograph

Yours s ncerely

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Department of Med c ne General Hosp tal
Park Row Nott ngham England

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Fig 1 ECG showing phasic voltage alternation

...re agree with Dr Arthur and colleagues that phasic alternation may well be very common in left sided thorax. A larger series would however be neces... establish the frequency.

...ding to our experience ECG is frequently per... in patients with left sided chest symptoms. This is ...on why ECG is a useful diagnostic tool in ...thorax—the ECG may demonstrate typical changes indicating the correct diagnosis which can subsequently be verified radiologically. However we do not claim that the diagnosis can be made exclusively electrocardiographically.

Yours sincerely
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Malmo General Hospital, Malmo, Sweden

BOOK REVIEWS

...*rine en Sekretion* 3rd revised edition. Edited ...abhart. 1079 pages, 411 illustrations, 35 tables. US $108.90. Springer Verlag (ISBN 3 540-...). Berlin, Heidelberg and New York 1978.

...for several years been the leading endocrinology ... in Continental Europe. This current and third ...has been considerably enlarged and the number of ...s who have been invited to write certain chap... considerable. Not only is their number but ...ality impressive. In spite of the fact that there ...contributors Labhart has succeeded to keep the ...composition of the book very homogeneous and as ...of fact he is himself the author of many chapters. ...ibus non est disputandum is an old and widely ...expression. The editor would be inclined to ...ble by saying that endocrinology is the flower ...al medicine. No other branch of our science deals ...ntly with Wirkstoffe active substances that are ...ade and therefore not foreign to the patients ...hormones in the widest sense of the word—and they ...ed in that sense by Labhart—are of course the ...rapeutic agents as they are selfmade. Nothing ...e satisfying than the substitution of a lacking .... Books that help us to discuss such problems ...entral place in the library of every physician.

...are many great qualities in this volume. Being a ...I should say that the emphasis on individual ...as exemplified by a large gallery of patient pic... one of the many excellent features of this volume. ...ows that the authors draw from a wide and well ...ed personal experience. In many susperscen... ...es it is maintained that the anecdotal, the individual ...le is important than large materials treated statis... ...n estigated with some modern biochemical or ...r biophysical method. The single patient judged ...d observer is still the basis of clinical medicine. ...t. This volume teaches us important lessons in ...ect.

...recent advances have been included. The refer... ...re remarkably complete and works from Euro... ...d American institutions have been quoted. It is ...sy to find individual papers that are missing ...h they have a central position in scientific discussions but this is also more or less a matter of taste. On the whole it is unusual to find a textbook that quotes studies from countries with many different languages. Also in this respect it represents the best Swiss tradition. The internist who is not a professional endocrinologist will note with great satisfaction that so-called tissue hormones and also the new family of neurohormones, by many regarded as neurological transmitters, have been treated extensively. The chapters on the hypothalamus, the gut and the pancreas contain excellent presentations from these fields. Also the introductory chapters on hormone activity are very well integrated into the general presentation even if in a way they belong to general physiology.

The book is highly recommended even if the price makes it inaccessible to many physicians' private libraries.

Jan G. Waldenstrom

Current topics in hematology, vol. 1. Edited by Sergio Piomelli and Stanley Yachnin. 247 pages. $24.00. Alan R Liss, New York 1978.

This is the first volume in a new series. It may well be that some colleagues are of the opinion that such progress reports in haematology have become too many. On the other hand the subjects treated in this volume and many of those planned for future volumes are of general interest to a large number of members of the medical profession at large.

This volume treats several important topics in haematology such as G6PD, haptoglobin, chelation therapy in hemosiderosis and red cell shape. The pediatrician will also find a short but concentrated discussion on the special characteristics of the red cell in the newborn. The most extensive chapter has Luzzatto as one of the authors. He is one of the world authorities on problems related to disturbances of glucose 6-phosphate dehydrogenase and the treatment of the subject is excellent. Not only are biochemical problems connected with the cause and effect of mutations in the gene that codes for

this enzyme discussed extensively Also the epidemiology in the widest sense of the word is treated with the aid of very interesting maps of the world The fact that G6PD—next to globin—is the most heterogenous protein molecule that we know of leads to many interesting hypotheses It could well be that these genes are really hypermutable It could also be that small differences are easy to detect In both instances such changes have led to differences in electrophretic mobility The third could be that such small changes are well tolerated or even have a selective advantage It is now a dogma that the last assumption is true but nothing contradicts the hypothesis genes may be less stable i e hypermutable It can be assumed that most G6PD variants are of single site mutations just like haemoglobin

The volume can be recommended to the interest in haematological problems Also will find a well written paper on the enzyme human neonate

Jan G Wa

ANNOUNCEMENT

The seventh annual meeting of The International Society for the Study of the Lumbar Spine will be held in New Orleans Louisiana USA May 24–28 1980 for members and invited guests

Non members wishing to submit papers for the program should communicate with the secretary Sunnybrook Medical Centre 2075 Bayview Toronto Ontario Canada M4N 3M5 Deadline stracts is Jan 15 1980

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Stroke Registration in Goteborg, Sweden, 1970–75

Incidence and Fatality Rates

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...ACT Strokes occurring among persons be... and 65 years of age (population 300 000) ... registered since 1970 in Goteborg Sweden ... of the validity showed that less than 10 % of ... of stroke were undetected During the period ...1970–May 14, 1975, 986 stroke events oc... 941 patients giving an annual average in... rate of 73 (89 for men and 58 for women) ...00 individuals 15–65 years of age The in... for all ages was estimated to be about 200/ The rates were higher for men than for ... all age groups There was a female ...erance for subarachnoid haemorrhage but a ...ponderance for other types of stroke In... rates increased with age, most rapidly for ...farcts and unspecified stroke Fatality rates ...at 3 weeks after onset of stroke they were ...subarachnoid and intracerebral haemorrhage ... for cerebral infarction and unspecified ...Incidence rates were lower than those found ...similar studies from Denmark and Finland, ... greater variations were found with respect ... of stroke Fatality rates were similar to those ... by other authors

...ds stroke incidence fatality rate type of stroke ...Med Scand 206 337 1979

...ovascular disease is the second most com... ...diovascular cause of death in Sweden (17) ...y other countries Often it is responsible ...here disability in survivors Cerebrovascular ...e as a public health problem was recognized ...HO meeting in Monaco in 1971 (19) and the ...for reliable and comprehensive information ...the incidence course and prognosis of stroke ...ent communities was stated The estab...ent of uniform registers of stroke patients ...commended (a) to provide information for epidemiological studies on a community basis concerning natural history in clinical terms and in terms of impact on the public health system and (b) to evaluate intervention measures such as 1) primary and secondary prevention 2) altered care in the acute stage of stroke and 3) rehabilitation

During 1971–75 18 stroke registers were established under the auspices of the WHO in various parts of the world Some results from these have been reported (1 10 14) Goteborg was one of the communities in which stroke registration was started This paper presents data on incidence and fatality in 986 cases of stroke occurring in the city of Goteborg during a 4½ year period from Nov 1970 onwards

BACKGROUND

In recent years programmes for the study and control of cardiovascular diseases have successively been implemented in Goteborg The emphasis is on ischaemic heart disease and hypertension The programmes include prospective population studies (2 15) a primary preventive trial (18) and secondary preventive trials in patients with myocardial infarction (7) As an underlying instrument of measurement a Myocardial Infarction Register has been in operation since 1968 (6) In 1970 the programme was extended to include registration of cases of stroke occurring in the community

Location of study Goteborg the second largest city in Sweden is mainly an industrial and commercial centre It is situated on the west coast and the climate is typically coastal with moderate differences between summer and winter

Population The total population of the city of Goteborg was 450 860 in 1970 and 445 704 in 1974 In 1970 13 % and in 1974 15 % of the inhabitants were aged 65 years and over In 1970 8 % of the population were aliens (41 % Finnish)

Organization of medical care Sahlgrenska Hospital (2 500 beds) dominated medical somatic care in the city until Dec 1977 and almost all patients with acute diseases

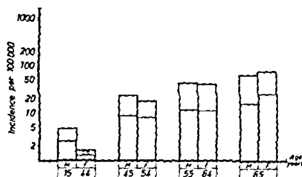


Fig 2 Intracerebral haemorrhage Age and sex specific incidence and mortality (hatched areas) semilogarithmic scale

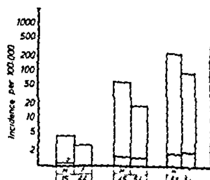


Fig 3 Cerebral infarction and unspecified ... Age and sex specific incidence and mort... areas) semilogarithmic scale

mation on disease manifestations was derived from sources other than the Stroke Register but the Register had been used for checking the diagnosis

The study of women in Goteborg (2) A representative sample of women aged 38–60 years (n=1 462) resident in Göteborg were examined during 1968–69 and 1974–75 Five cases of stroke were reported among them after 1970 and all had been entered in the Register

The primary preventive trial (18) One third of all male residents of Goteborg aged 47–54 years (n=7 454) were screened during 1970–73 and rescreened 4 years later during 1974–77 By 1976 34 cases of stroke had been reported by participants since 1970 When checking with the patients or examining their case histories 18 of these men did not fulfil the criteria for entry in the Stroke Register while 15 had been registered as stroke cases and one patient with stroke fulfilling the criteria had not been registered An approximate detection rate of 15 (94%) out of 16 cases of stroke in this population was thus indicated

The Tynnered project (16) All visits to general practitioners in a defined district of Göteborg were recorded and coded according to diagnosis during 1974–76 The diagnosis of cerebrovascular disease ICD code 430–438 accounted for 12 consultations by six patients aged below 65 years during this period Their case histories were examined and in none of these cases had a stroke occurred after Nov 1970 according to our criteria Thus no lapse in register coverage could be demonstrated in this way

Screening of 70 year old people in Goteborg (12) One third of all residents of the city aged 70 years were screened in 1971–72 During 197? some ... persons) were questioned concerning stroke ... physician s interview Thirteen gave a p... and seven of these said they were admitted ... the time of the stroke This is a lower f... expected for hospital admission of stroke ... figures are uncertain however as the diagn... was not further verified in these cases and t... was older than that of the present study

RESULTS

During the period Nov 15 1970–May 1... cases of stroke occurred in 941 patie... years resident in Göteborg The *...* *annual incidence rate* (attack rate) per 1... viduals aged 15–65 years was 73 (89 f... 58 for women) This *difference* ... (p<0 001) If only first strokes are co... incidence rate was 65 (77 for men ... women)

The number of stroke cases and ... by age group and sex are shown in T... rates were higher for males than for f... age groups

The incidence rates for each type of ...

Table IV *Number of cases of stroke and accumulated case fatality rates (F R %) in G...*

	No of stroke cases	Dead at 3 weeks		Dead at 1 year		Dead at 2 years*	
		No	FR	No	FR	No	FR
Males	602	147	24	193	32	57	46
Females	384	133	35	161	42	44	47
Total	986	280	28	354	36	101	4?

* 216 cases with onset of stroke in 1971 were followed for 2 years

Number of cases of stroke and fatality rates (FR %) at 3 weeks by age group and type of stroke in 1970–75

	Subarachnoid haemorrhage		Intracerebral haemorrhage		Cerebral infarction		Unspecified type		Total	
	No	FR	No	FR	No	FR	No	FR	No	FR
	4	38	24	58	24	4 2	1	0	91	34
	64	47	50	72	67	12	31	6 5	212	36
	66	45	102	65	170	15	262	10	600	25
	9	67	14	71	25	24	35	11	83	31
	181	45	190	66	286	14	329	10	986	28

r both sexes are given in Table II The y small number of cases of unspecified the youngest age groups was the result of tensive diagnostic work up in these groups ly large proportion of subarachnoid and ebral haemorrhages is mainly explained by e age of the study population The increase ence with age was very steep for brain in nd unspecified stroke while it was much nced for subarachnoid haemorrhage and rebral haemorrhage

ale/female ratios of incidence rates for e of stroke by age group are shown in Table e sex ratio varied between types of stroke arachnoid haemorrhage there was a fe preponderance whereas for intracerebral ge the ratio varied from a male pre n the youngest to an almost equal dis n the oldest age group For cerebral in and unspecified stroke the male preponder as pronounced in all age groups The differ incidence rates between the sexes was sig for subarachnoid haemorrhage cerebral in n and unspecified stroke regardless of age 01) A great difference between the sexes in e group 15–44 was found also for intracerebral rhage ($p<0\ 01$) The male/female ratio of l incidence rates showed a male preponder which increased with age reflecting the in g proportion of brain infarcts with a high preponderance among older stroke patients incidence rates by age group for each type of are shown in Figs 1–3 brain infarction and ified stroke being considered together The se in brain infarcts and unspecified stroke ge seemed to manifest itself a decennium later men than in men

alysis of the *case fatality* rate shows that most deaths occurred within 3 weeks of onset of stroke After 3 weeks and up to one year only 8% died The overall case fatality rate at 3 weeks was 28% at one year 36% and at 2 years 47% (only stroke patients with onset during 1971 were followed for 2 years) (Table IV) As most deaths occurred within 3 weeks the case fatality rate at 3 weeks was used for all further fatality analyses The accumulated case fatality rate by sex showed a higher early mortality in women than in men This was accounted for by a comparatively larger proportion of subarachnoid haemorrhages in female stroke patients At 2 years this difference disappeared

Fatality rates (at 3 weeks) by age and type of stroke are given in Table V No particular differ ences seemed to exist between the sexes or the age groups but there was a pronounced difference be tween different types of stroke with a high fatality rate for subarachnoid haemorrhage and particularly for intracerebral haemorrhage and a much lower fatality rate for cerebral infarction and unspecified stroke The corresponding mortality rates can be calculated from the fatality rates in Table V and the incidence rates in Table II and are shown in Figs 1–3

Analysis of incidence of stroke and fatality rates by year of registration did not seem to indicate any change with time in incidence rates at large but some decrease in individual types of stroke was noted for both sexes in morbidity from subarach noid haemorrhage and intracerebral haemorrhage and an increase in cerebral infarction and un specified stroke There was no discernible differ ence between the age groups in these respects There was a small decrease with time in case fatali ty for men with subarachnoid haemorrhage and in cerebral infarction and unspecified stroke for both sexes There was no apparent decrease in the in tracerebral haemorrhage fatality rate

Table VI *Annual incidence of stroke by sex per 100 000 inhabitants in selected comm[illegible] group 45–64 years*

Community	Years of study	Males		Females	
		45–54 y	55–64 y	45–54 y	55–64 y
Rochester Minn USA (11)	1955–69	158	511	71	261
Espoo Finland (1)	1972–73	206	495	143	250
Fredriksberg Denmark (14)	1971–73	–	450	–	190
Göteborg Sweden (present study)	1970–75	97	316	65	[illegible]

DISCUSSION

Goteborg is well suited for studying the epidemiology of stroke The city has a well defined population and an accurate census which is updated at two week intervals *Studies of acute cerebrovascular* diseases constitute an integral part of the established programmes for the epidemiological studies of other cardiovascular diseases in Göteborg Until recently only one hospital received emergency cases of somatic illness and by tradition patients with acute illnesses in Swedish cities primarily contact a hospital

Limiting registration of stroke to subjects up to 65 years of age further increases the likelihood that these patients in fact received hospital care from the onset of symptoms Furthermore stroke occurs more often as the sole symptom of disease in younger than in elderly persons Hence the cerebrovascular disease with associated factors can probably be more accurately studied in younger subjects

On these grounds there were good reasons to believe from the outset of the study that detection of stroke in the population would be effective by the methods used The validation procedures were per[illegible] to show the degree of detection of cases of stroke in the population during the study These checks showed that no patients with stroke were treated wholly outside hospital that 90–95 % of stroke cases treated in hospital were registered and that approximately 95 % of all cases of stroke in the population were registered as judged from population screenings The number of undetected cases in this study would therefore not alter the figures substantially There was no indication that these constituted any particular group of stroke cases

The crude incidence rate in this series for the age groups concerned is somewhat higher than in a previous report (10) even when recalculated for the ages 15–65 The difference may well be [illegible] proved case detection in the present [illegible]

To estimate the *total incidence of* [illegible] population irrespective of age is di[illegible] ing to a study from 1963 (3) about [illegible] *stroke patients in Goteborg were under 6*[illegible] age and the total incidence for Goteborg [illegible] estimated to be approximately 150 per 1[illegible] However the age composition of the p[illegible] changes an increasing proportion be[illegible] years of age and people below 65 yea[illegible] probably now account for less than one [illegible] cases of stroke A reasonable estima[illegible] incidence of stroke for Goteborg migh[illegible] about 200 per 100 000

Comparison of the total incidence with [illegible] other studies is not possible but where [illegible] ing fits with the present series the ag[illegible] dence rates are comparable with those [illegible] series (1 5 8 11, 13 14 20) mainly [illegible] later Our findings suggest a somewhat [illegible] dence rate in Göteborg than in several [illegible] for the age groups 45–54 and 55–64 (Ta[illegible] incidence rates in Göteborg are above [illegible] than the figures reported from Finland [illegible] (1) which were obtained by an [illegible] istration technique This also applies [illegible] parable figures from Copenhagen [illegible]

It should be noted that the incidence f[illegible] Goteborg include all stroke man[illegible] recurrent strokes in some individuals [illegible] The figures from Rochester USA (11) [illegible] first strokes only and those from Finland [illegible] mark numbers of persons experienc[illegible] more strokes during the study period [illegible] that the figures from Goteborg are [illegible] estimates To compare incidence fi[illegible] ester from 1955–69 is questionable as the [illegible] there may well have continued to [illegible] then

Avera e annual incidence rate by type of stroke per 100 000 inhabitants in selected communities group 55–64 years

	Subarachnoid haemorrhage	Intracerebral haemorrhage	Cerebral infarction + unspecified type	Total
and (1)	49	67	243	358
g, Denmark (14)	16	36	247	299
Sweden (present study)	27	41	173	241

s differ greatly between reported series whole there is a male preponderance eases with age This was also the case in t series This probably reflects the fact lative frequency of brain infarcts in ore rapidly with age in men than in

n rates reported here are close to those ther investigators (1 8 11 13 20) both fa ality and for fatality specified by age e of stroke The outstanding differences ively young cases are those between the oke and not between the age groups or

s of stroke in this series showed a vary e with age and varying sex ratios There ver an evident similarity between cere ion and unspecified stroke for increase well as for sex ratio and for fatality rate that although diagnostically uncertain ified stroke group could be considered ith cerebral infarction in this connec jo g stroke patients the proportion hnoid haemorrhage and intracerebral e was relatively large and the fatality he eas for older patients the fatality rate owing to a large proportion of these ing caused by brain infarcts (+un troke) It seems evident from these in sex ratio increase in frequency and in fatality rate that subarachnoid se intracerebral haemorrhage and cere ion/unspecified type of stroke constitute isease entities even in epidemiological

son with other series with respect to type is of special interest in the search for l clues but hazardous when diagnostic y Age and sex specific incidence rates for individual types of stroke are comparable however when similar criteria of diagnosis of type are used as in the present study and the studies in Finland (1) and Denmark (14) Incidence rates for each type of stroke for the age group 55–64 years are shown in Table VII There are not only obvious differences in the total incidence rates but even more so between the individual types of stroke (note that the figures from Goteborg include recurrent strokes) These differences can hardly be ascribed solely to inconsistencies in methodology between the centres These figures indicate rather that real differences in risk of stroke may exist between these communities They are consistent with data from the registers of coronary heart disease in Finland and Sweden showing that in 1971 the incidence of acute myocardial infarction was 2–3 times higher in Helsinki than in Goteborg (9) Mortality rates from vital statistics show that for the age group 55–64 years the mortality from stroke in 1972 was twice as high in Finland as in Denmark and Sweden for both sexes individually and combined the latter two countries having very similar death rates So far the prevalence of hypertension and other cardiovascular risk factors in the three communities is known only to a limited degree and comparisons are not possible Furthermore it is not known how the risk factors influence the distribution by individual type of stroke in each community There has been a great deal of interest in prevention (treatment of hypertension antismoking measures dietary advice) for the last 10–20 years in Goteborg but it is not known to what extent these measures have been effective

The three major types of pathophysiological processes in stroke seem to correspond to three disease entities each with its own clinical and epidemiological characteristics Different aetiological factors may operate to varying degrees in each

Furthermore preventive measures need not necessarily influence the total stroke morbidity but may still affect one or more of the types of stroke

Unfortunately studies of sufficiently large numbers of cases with reliable and comparable diagnosis of type of stroke are difficult to achieve Knowledge of fatality rates and sex ratios together with age specification might to some extent make it possible to discriminate between the important types of stroke so as to allow comparison between different series But this will be possible only when the detection of cases of stroke in the population is known and close to total so that true incidence figures are obtained *Mortality figures* even if age and sex specific cannot reflect the composition of morbidity with regard to type of stroke and are therefore of limited value

ACKNOWLEDGEMENTS

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Effect of Prolonged In Vivo Administration of Leukocyte Interferon on the Mitogen Responsiveness of Human Lymphocytes

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[ABSTR]ACT Peripheral lymphocytes from patients [with osteo]sarcoma receiving interferon (IF) as adju[vant ther]apy were tested in vitro for response to var[ious mitogens]. Prolonged parenteral administration [of IF prep]arations caused no major change of the [mitogen re]sponses. The ability of IF when added in [vitro to in]hibit lymphocyte response to mitogens was [not affecte]d to any major extent by in vivo administra[tion].

[Key words: i]nterferon lymphocytes mitogens

[Acta Med] Scand 206 345 1979

[Since 19..] more than 100 patients with various [malignant] diseases have received interferon (IF) at [Karolins]ka Hospital. In late 1971 a clinical trial [was start]ed with the object of examining the effect [of IF th]erapy in patients with osteosarcoma.

[Among] other effects on the immune system (7) [IF prepar]ations have been shown to suppress lym[phocyte res]ponse to mitogens and allogeneic cells [...] 1). The evidence that IF may interfere [with lymph]ocyte functions prompted a study in a [group of th]ese osteosarcoma patients of 1) whether [the admini]stration of IF affects the reactivity of [periph]eral lymphocytes to mitogens and 2) [whether thi]s therapy modifies the capacity of IF to [inhibit mit]ogen responses in vitro.

STUDY POPULATION

[This study compri]ses 20 patients (5 females 15 males) with [osteosarcom]a of the long bones without evidence of [metastases] on admission who received IF as adjuvant [therapy. Th]e ages ranged from 7 to 30 years (mean 19). [When] a control group was used it comprised [members] of the Laboratory staff (9 men 5 [women]) in an age range of 26–61 years (mean 34).

METHODS

Treatment

Human leukocyte IF (see below) was given f[or a] per[iod of] 18 months after primary surgery (amputation, exarticula[tion] or resection). To 9 of the 20 patients local [irradiation] was given (4000–6500 rad) prior to surgery. The IF was administered by intramuscular injection 3 times a week except during the first months and if the patient [c]ame to the hospital when it was given once a day. Each [injec]tion consisted of 3×10^6 IF units (14). The IF therapy [was] discontinued in some patients when metastases [de]veloped.

Blood sampling

When the patients were tested before IF therapy the blood sample was collected after biopsy but before major surgery. From patients receiving radiotherapy blood was drawn when this treatment had been completed. During IF therapy blood was collected 24–72 hours after the last injection.

Separation of lymphocytes

Lymphocytes were separated from heparinized venous blood by centrifugation on a layer of Ficoll Isopaque (11) and washed twice by centrifugation in Eagle's minimal essential medium (MEM) supplemented with 10% of heat-inactivated human serum (HS) from AB donors. Approximately 90% of the cells were classified as lymphocytes after crystal violet staining, the rest as monocytes and granulocytes.

Mitogens

The contents of vials containing phytohaemagglutinin (PHA, Bacto Phytohaemagglutinin M, Difco Lab, Detroit, USA) and poke weed mitogen (PWM, Grand Island Biological Company, NY, USA) were dissolved in 5 ml of MEM. These solutions will be referred to as 100% of PHA and PWM respectively. Concanavalin A (Con A, Sigma Chemical Co, St Louis, USA) was dissolved in MEM.

Abbreviations: IF interferon, MEM Eagle's minimal essential medium, HS human serum, PHA phytohaemagglutinin, PWM poke weed mitogen, Con A = concanavalin A

Table I *Mitogen response of peripheral lymphocytes to PHA PWM and Con A before* [illegible] *IF therapy*

Mitogen	Concentration	Incorporated ^{14}C thymidine (cpm)				
		Patients (n=11)		Controls (n=14)		
		Mean	S D	Mean	S D	p
PHA	1 5%	100 600	10 100	71 700	5 600	<0 01
	0 75%	85 200	9 500	57 200	7 900	<0 05
PWM	1 0%	26 600	4 700	30 100	1 400	NS
	0 1%	27 900	5 800	36 900	3 600	NS
Con A	14 0 μg/ml	65 200	8 600	74 500	5 400	NS
	3 5 μg/ml	33 400	6 500	40 600	4 900	NS

NS=not significant

Cell culture conditions and thymidine incorporations

Details of the culture conditions and the measurement of incorporated radioactivity have been published elsewhere (4) Briefly 2.5×10^5 lymphocytes were cultured in glass tubes containing 1 0 ml of MEM supplemented with glutamin 125 units of penicillin 125 μg of streptomycin and 10% of heat inactivated HS Various concentrations of mitogens were added to some of the cultures others served as controls IF was added to some tubes at the beginning of the culture period at a final concentration of 1 000 units/ml After 4 days of incubation at 37°C in a humidified 5% CO_2 air atmosphere 0 4 μCi of ^{14}C thymidine (specific activity 54 mCi/mM) was added to each culture The cultures were comple ed [illegible] and the radioactivity of the material pre [illegible] trichloroacetic acid was measured by liq [illegible] and expressed in cpm

Means of duplicate cultures were cal [illegible] arithmetic basis Values for cultures w [illegible] were subtracted from the values obta ned f [illegible] sponding cultures with mitogen added

IF preparations

The methods used for the production of the le [illegible] preparations and the measurement of the [illegible] tivities have been described elsewhere ([illegible]

Table II *Effect of IF therapy on lymphocyte counts and mitogen responses in vitro presented* [illegible] *between values during and before II therapy*

	Months of IF therapy before 2nd test	Relative lymphocyte count (%)	Relative mitogen response (%)						[illegible]
			PHA (%)		PWM (%)		Con A (μg ml)		
			1 5	0 75	1	0 1	14	3 5	
	3	59	176	241	193	359	60	460	4 000
L	3	71	98	62	103	67	93	73	-
J B	5	74	92	87	83	44	60	33	6 400
A R	18	86	71	49	117	56	174	133	4 000
U H	10	99	151	79	64	67	116	52	4 000
B S	9	82	42	35	101	67	65	32	-
S L	17	114	94	83	97	86	1 0	105	6 400
O K	12	39	15	50	70	88	10?	84	-
L E	15	87	199	279	100	92	11	86	-
Median	10	82	94	79	100	67	116	84	
96% confidence limits	3 2	40 0	15 2	15 2	64 1	44 9	60 2	33	
p		NS	NS	NS		<0 05	NS	NS	

* Months after initiation of IF therapy FM=free from metastases at the latest control 3–6 years after [illegible] therapy IC=death in intercurrent disease

NS=statistically not significant

Effect of w l dra al of IF tl erapy on lympl ocyte co it and m togen response i v tro presented between al es d r ng and after IF tl erapy

[illegible] ons were made 9–18 months after n t at on of IF therapy wh ch lasted for 18 months

Months between withdrawal of IF therapy and 2nd te	Relative lymphocyte count (%)	Relative mitogen response (%)						Ir rad at on (rads)	Me a e
		PHA (%)		PWM (%)		Con A (μg/ml)			
		1.5	0 75	1	0 1	14	3 5		
3	44	66	59	40	1?	4?	18	4 000	FM
3	1 4	111	71	77	51	78	89	4 000	FM
4	184	110	76	151	47	118	78	4 000	
5	39	304	500	118	10?	365	5?5		FM
5	149	122	167	51	77	47	67	6 800	
5	?33	?83	3?9	183	?79	1?6	16?	4 000	F 1
5	103	81	73	104	97	11?	174	6 400	F 1
6	146	37	39	98	71	14	?5		
7	9?	234	76	5?	95	34	11		3
5	124	111	76	98	77	8	78		
36	39 ?	37 3	39 3	40 2	12 1	14 ?	11 ?		

the hanges are sta stically s gn f cant
after in tiation of IF therapy FM free f om metastases at the latest control 3–6 years after n t a on o

[illegible] ed e ther concentrated IF or partially purif ed spec f c act v ties of approx mately 2×10^4 and [illegible] units mg of pro e n respect vely Preparat ons IF were used for the n vitro expenments

[illegible]

A considerable intertest variab l ty of the m togen s of human lymphocytes even when the lympho- obtained from the same donor and are tested [illegible] cond tions To reduce th s variab l ty each patient s lymphocytes was accompan ed by a [illegible] of lymphocytes f om one of two healthy control The m ogen reactiv ty of the pat ent s [illegible] was expressed as a pe centage of the value [illegible] control lymphocytes

[illegible]

[illegible] presen ed in Table I were analysed w th a test [illegible] type For the results in Tables II III and [illegible] was appl ed to test the hypothes s of a change equal to one against a two s ded alterna

RESULTS

IF he apy on the lymphocyte and m ogen response

[illegible] ogen responses of the pat ents lymphocytes [illegible] en ed as relat ve values (see Methods) Ta [illegible] owever g ves the absolute [illegible]C thym d ne [illegible] tions obtained before in tiation of IF and major surgery n 11 osteosarcoma pa tients and 14 healthy controls The respon e f th pat ents lymphocytes to PHA was s gn f can l higher than that of the controls The two group were however not matched for age and sex No sign ficant d fferences could be detected us ng the other m togens The lymphocyte counts before surgery and IF therapy ranged from 1 300 to 3 300 cells/μl of blood (mean 2?00) (normal range 800–4 000)

In 3 pat ents lymphocyte counts and relat ve mitogen responses were exam ned before during and after IF therapy (Fig 1) Two of these patients (A R and S L) received radiotherapy prior to surgery All 3 pat ents rece ved IF during 18 months and were st ll free from d sease 3–5 years after in t ation of IF therapy In these 3 patients the lym phocyte counts rema ned essent ally unchanged Mitogen responses exhib ted large variations but there was no consistent pattern of the changes

The lymphocyte counts and m togen responses were determined in 9 pat ents before and 3–15 months after introduct on of IF therapy (Table II) There were no major d fferences between the m togen responses recorded on the two occas ons with the poss ble exception of PWM at a concentra t on of 0 1% There was a reduct on of lymphocyte counts after in tiat on of IF therapy but th s was not significant There were no major differences in

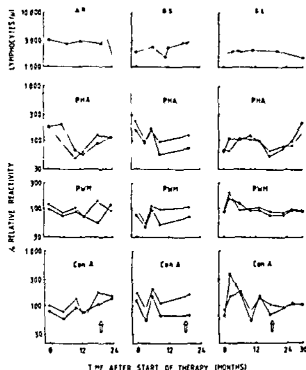


Fig 1 Effect of prolonged administration of IF on the lymphocyte counts and responses to mitogens in 3 patients Mitogen responses are expressed as a percentage of the corresponding values of a control PHA 0 75% (O—O) 1 5% (×—×) PWM 0 1% (O—O) 1% (×—×) Con A 3 5 μg/ml (O—O) 14 μg/ml (×—×) Arrow indicates withdrawal of IF therapy

either lymphocyte counts or mitogen response between the patients who had received radiotherapy and those who had not Three of the patients developed metastases while receiving in vivo administration of IF and one died in intercurrent disease

The lymphocyte counts and mitogen responses of ...tients during and after IF therapy (3–7 months ...er withdrawal) showed no significant differences ...Table III) There were no major differences between the patients who had received radiotherapy and those who had not

Effect of IF therapy on the inhibitory activity of IF on mitogen responses in vitro

The inhibition of the mitogen response by IF in vitro (1 000 units/ml) was tested in 2 patients before during and after IF therapy One of them (A R) had received radiotherapy prior to IF therapy No consistent pattern of changes in the ability of IF to inhibit mitogen response in vitro were observed in these two patients (Fig 2)

The ability of IF when added in vitro ... lymphocytes response to mitogens was ... patients before and during IF therapy (Ta... Apart from a significant reduction of the ... IF to inhibit the response of the lymphocy... of the PWM concentrations used no sta... significant changes due to IF therapy cou... There were no major differences betwe... tients who had received radiotherapy a... who had not

DISCUSSION

Since IF became available for clinical use a ... of trials have been conducted with the ... examining its effect on various neoplast... diseases (6) It is therefore importa... whether IF can interfere with normal bod... tions

The results of experiments on laborat... and of in vitro studies on human peripheral l... cytes have demonstrated that IF can ... several functions of lymphocytes The ... of the present investigation was to stud... administration of IF impairs the functional ...

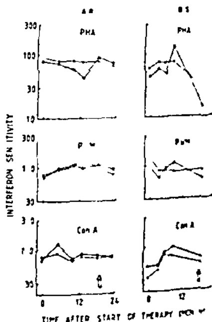


Fig 2 Effect of in vivo administration of IF on ... hibitory action of IF in vitro on lymphocytes ... PHA PWM and Con A in 2 patients The ... ty of IF was determined as the percentage ... stimulation cultures with IF (1000 ... the corresponding values for cultures ... as in Fig 1

R E tof n s adm n str it on c f IF t II e c b l ts of II s l en a lded in s tr t t o t r p phon es o m t gens

ts were cal ula ed as percentage nh b t on of stimulat on in cultures conta n ng IF (1 000 un ts/ml) comp red cultures w thout IF The tests were performed before IF therapy and 3–18 months after in t ation of IF th e t st e is ub racted from the second A negative value thus ind cates that the lymphocytes ha e becom r to IF

Months of IF therapy before nd test	Change n ab l ty of IF added in v tro to inh b t lymphocyte response to m togens: PHA (%) 1 5	PHA (%) 0 75	PWM (%) 1 0	PWM (%) 0 1	Con A (μg/ml) 14	Con A (μg/ml) 3 5	Ir rad at on (rad)	Meta ta es
3	+19	+52	65	−42	+17	+15	4 000	
3	+ 7	8	−25	16	+ 5	+26		IC
5	20	23	−20	− 2	−13	12	6 400	
9	15	−86	+57	10	38	50		FM
10	+37	+19	21	21	+ 3	55	4 000	
12		+10	+37	90	+18	20		FM
15	+51	+35	+ 7	+ 4	5	8		FM
18	+13	−11	9	−41	+ 4	13	4 000	FM
9 5	13	1	−14 5	18 5	3 5	12.5		
fidence 13	20 4	86 4	−65 4	90 4	38 2	55 2		
	NS	NS	NS	$p<0\ 05$	NS	NS		

h after in tiat on of IF therapy FM free from metastases at the latest control 3–6 years af e n t at on o I IC death n n ecurrent d sease
a r PHA at 1 5% concentrat on where a 87 5% confidence l m t is shown
tistically not s gn f cant

pheral lymphocytes S nce IF in vitro inh b ts ponse of human peripheral lymphocytes to m gens (4) the effect of prolonged in vivo stra on of IF on th s react on was studied g in v o adm n trat on of IF there were no t cha es in the lymphocyte counts or their es to m ogens (Tables II and III) Owing to tau ely large inter and intrasubject vari n m m ogen response small changes in this ty that m ght have occurred during in vivo ration of IF w ll probably not have been N one heless if IF therapy does exert any e effects on the m togen responsiveness of ocytes these effects are relat vely small of the pa ents had received local rad ation which s known to induce lymphopenia (3) do not seem to be any d fferences e ther in ocyte counts or n m togen responses be e the s who had or had not received radia hera y (Tables II and III) but the pat ent is small a d th s conclus on therefore uncer

ab l y of IF when added n vitro to inhib t togen responses of lymphocytes was not altered to any major extent by in vivo adm n stra tion of IF (Fig 2 Table IV) This find ng supports the conclusion that the in vivo administrat on of IF had no major effect on the m togen response of the lymphocytes

It has been shown in the mouse that there is an optimal dose range for the ant tumor activity of IF too h gh doses may cause atrophy of lympho d or gans and shorten the survival time (7) If IF has antitumor activity in man it is therefore important that opt mal doses are given We do not know whether IF administered in h gher doses than for the osteosarcoma pat ents (3×10^6 un ts of IF da ly or 3 t mes a week) has any suppress ve effects on the immune system

In conclus on long term in vivo admin strat on of leukocyte IF in the doses used in th s study does not seem to change the m togen responsiveness of the peripheral lymphocytes to any detectable ex tent

ACKNOWLEDGEMENT

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Acta Med Scand 206 351 360 1979

Risk Factors for Myocardial Infarction in the Stockholm Prospective Study

A 14 Year Fcll p F ct ss t o t ll c R lc c f Pl ts Tr gl cerides an l Cl olester l

Lars A Carlson Lars Erik Bottiger and Per Erik Åhfeldt

From K ng Gus af V Research Ins t e and tl e Dep tment f In ernal Med c ne Kar l n ka H sp tal St ckl oln S eden

ACT A 14-year follow up of the Stockholm ... the study is reported A number of 130 new ... dial infarctions (MI) were found in a pro- ... group of men (n = 3 189) and another 46 i e ... 1 6 MI in the total group (n 3486) D f ... types of mult variate statist cal analyses show ... blood pressure smoking fasting plasma ... rations of cholesterol and triglycerides ESR ... were independent risk factors for MI while ... the height index was not Elevated BP became ... rtant risk factor only after the age of 50 ... ch age BP smoking and the two plasma ... were en ered into the logistic multivariate ... plasma triglycerides were more important ... sk factor than cholesterol Quintile analysis ... that the rate of new MIs increased more with ... ng triglyceride than increasing cholesterol ... In the prospect e group the average rate of ... ls for men below 60 years was 32 per 1000 ... ottom and top qu nt le these rates were 16 and ... plasma triglycerides and 27 and 47 for choles- ... When the men were divided into 4 groups ... gard to both plasma l p ds the rate of new ... creased successively from group to group ... his chain both l pids normal only cholesterol ... ly triglycerides h gh and both plasma lipids

... b ood p essu e erythrocyte sed mentat on ... og ob n mu tivaria e analys s myocard al n ... la ma choles e ol plasma triglycerides pro- ... t ud n k f ctor smok n g

... Med Scand 206 351 19 9

... m of he S ockholm Prospective Study (SPS) ... h started in 1961 was to gain informat on ... e el on between fast ng plasma triglycer ... d cho es erol values and the future develop ... f schaem c heart d sease (IHD) The reason for this was our f nd ng reported in 1960 th Stockholm survivors of myoc rd al nfa (MI) not only had a h gh frequency of el plasma cholesterol values but also of ra ed pl triglyceride levels (9) wh ch then was a new servation Two other reports w th the same c l appeared at that t me (3 4) Our f rs follow p SPS after n ne years comprised 71 cases of n MIs and ind cated that both plasma chole ter l n plasma triglycerides were risk factors for IHD 11

Th s second report which is based upon 176 ne male infarcts in the total group—whereof 130 in the prospective group—with a follow up of 14 years corroborates the prelim nary f ndings (11)

STUDY POPULATION

The n t al des gn of the study and the cl n cal and laboratory methods have been described in deta l (1?) The study populat on is composed of the cl entele of a health survey center an organ zat on wh ch offers the r employees a yearly health check up

The follow ng exam nat ons and analyses were n cluded *Case h story* w th spec al emphas s on d seases and hab ts of potent al interest n relat on to the development of IHD *We gl [he gl t ndex* calculated as we ght (kg)/(he ght (cm) m nus 100) *Sys ol c and d astol c BP* measured w th a mercury manometer at the end of the exam nat on *ECG* at rest w th standard leads and f ve chest leads (CR -CR, and CR) *Cl est ad ogram* was read by a rad olog st *Haemoglob n* was determ ned as oxyhaemoglob n *ESR* was determ ned according to the orig nal Westergren method *U ne* was tested for the

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Abb e at ons SPS = Stockholm Prospect ve Study MI myocard al nfarct on IHD = schaem c heart d s ease CVA = cerebrovascular acc dent VLDL very low dens ty l poprote n LDL low dens ty l poprote n HDL = h gh dens ty l poprote n

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... Number of men with different categories of MI

... first incidence is included

	Prospective group ($n=3\,189$)	Pre-existing disease group ($n=297$)	Total group ($n=3\,486$)
...ers	72	17	89
...	34	22	56
... death	17	6	23
... dead	7	1	8
...	130	46	176

... smoker=1 quit smoking previously heavy ... moderate smoker (<20 cigarettes/day)=3 ...ker=5 Age was introduced as years raised to ... power in all regression analyses as this gave ...est r-value and triglycerides as log concen... due to their skew distribution The multiple regression analysis was carried out with a com... program which first chooses the independent ... with the highest correlation with the dependent ... and then step by step the variable still outside ... equation which has the highest correlation ... this variable into the multiple regression equa...

...al calculations were those recommended by ...(12) unless otherwise indicated

RESULTS

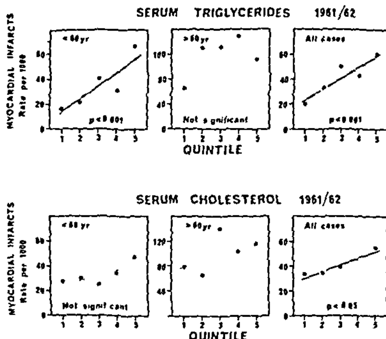
Causes of death

In the total group 535 men and 163 wom... h... died The causes of death were (no of men ... women) malignant tumours 156/74 MI as d... above 104/13 other IHD and heart diseases ... 18 CVA 39/19 gastrointestinal diseases 2... vascular disease including thromboembolism 2... respiratory disease 21/3 suicides 18/2 accid... 15/5 others 19/13 The causes of death in the total material and their relations to risk factors for MI will be dealt with in a forthcoming study

... Characteristics of subjects in the prospective group later developing MI (mean ± S E M)

	All MI			MI alive	MI dead	All healthy 50-59-year old men*
	All ages	<60 y	>60 y			
	130	91	39	72	58	
	54 4 ±0 7	51 0 ±0 6	63 8 * ±0 5	52 7 ±0 9	56 5*** ±0 9	
...d event	96 ±4	102 ±5	78 ±7	98 ±5	93 ±7	
...rides ...)	1 71 ±0 07	1 80 ±0 08	1 45** ±0 10	1 71 ±0 09	1 70 ±0 10	1 46
...rol ...ml)	295 ±6	297 ±7	289 ±11	300 ±6	287 ±10	278
...height index ...=100)	0 98 ±0 01	0 97 ±0 01	1 00 ±0 02	0 99 ±0 01	0 97 ±0 01	0 95
... BP (mmHg)	149 ±2	147 ±2	157 ±4	148 ±3	151 ±3	138
...ic BP	92 ±1	92 ±1	93 ±2	92 ±2	91 ±2	88
	91 ±0 6	92 ±0 6	89 ±1 2	91 ±0 7	90 ±0 9	89
...n/h)	8 7 ±0 7	7 3 ±0 6	12** ±2 0	6 7 ±0 7	11 0** ±1 3	6 5

...p 10 in SPS (12)
...05 $p<0.01$ $p<0.001$ Differences were tested between the two age groups and between MI alive and MI ...d any significant difference indicated



F g 1 Rate of MI in in d fferent age groups at the 1s up in relation to the fas centrations of triglycerides terol in 1961-62 The result of a sion analys s is also g en

Categories of MI (Table I)

In the prospective group 45 % died at the first IHD manifestation The corresponding figure for those with pre existing disease was 61 %

Initial characteristics of IHD subjects

Table II shows some of the initial characteristics of subjects later developing IHD Mean serum lipid values and BP were higher than in the entire popula tion There were certain differences between IHD cases below and above 60 years of age which can not be due to differences in age Particularly strik ing from the risk factor point of view ar serum triglyceride values for the cases

There were no major d fferences be alive or MI dead except that the la and had a higher FSR

Single risk fact or analysis

In the prospective group the ra e of creased with increasing con entrations plasma triglycerides and choles erol as the quintile statistics (Fig 1 and Tab

Table III *Single regression analysis of rate of MI (per 1000) on q untile number for seven variables (prospective group)*

	Cholesterol		Tri glycerides		We ght/height index		Systol c BP		Diastol c BP		Hb		FSR
	All	<60 y	All	<60 y	All	<60 y	All	<60 y	All	<60 y	All	<60 y	All
a^1	25	20	15	3	32	30	28	21	?7	21	22	13	[illegible]
b^2	5 2	4 3	8 7	10 6	3 0	0 9	4 3	4 0	4 7	4 0	6 3	6 4	[illegible]
t^3	2 1	1 7	3 6	4 3	1 2	0 4	1 7	1 7	1 9	1 6	2 4	2 1	[illegible]
p^4	*	ns	*	**	ns	ns	ns	ns	[illegible]	ns	[illegible]	*	*

[1] Intercept on the y axis
[2] *Linear regression coefficient rate of infarcts (per 1000) per quint le*
[3] *t* Value for the signif cance of the regression coefficient
[4] Statistical signif cance of the *t* value ns = not s gn ficant ($p > 0.05$) * p 0 05 ** $p < 0.01$ *** $p < 0.00$

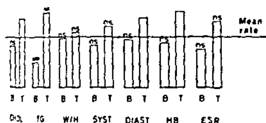


Fig 2 Rate of MI in th p o p t group in the bottom (*B*) and the t n quintile for serum cholesterol (*CH*) and triglycerides (*TG*) weight height index (*W/H*) systolic (*SYST*) and tolic (*DIAST*) BP Hb (*HB*) and *I* Statistical significance was tested f quintile against the remaining four qu tiles combined i e *B* against 2–5 against 1–4 The χ^2 test was used Yates correction $p<0.05$ * * $p<0.001$

the in rease as well as its significance was L pronounced for triglycerides with a four fold from th bottom to the top quintile in the p <60 years Furthermore the quintile analysis showed that the rate of MI rose easing values for diastolic BP Hb and ESR I) The weight/height index was however ctor for IHD

et analysis is given in Fig 2 which shows of infarction for the top and bottom quin imilar picture as above is obtained It is striking to see that there is not only an risk for MI with high triglycerides but ificantly reduced risk with low tri s The weight/height index on the other variable in which both the bottom and top have rates of MI very close to the average per 1000 for the entire prospective group lysis of non numerical parameters is given IV Smoking as is well known carries a ntly increased risk for IHD Neither physi ty nor position at work had any significant e on the rate of development of MI High f education however appeared to protect IHD

Multiple risk factor analysis

The results of multiple logistic regressi including the most commonly studied risk viz BP smoking and serum cholester serum triglycerides are given in Table V type of analysis age and systolic BP we most significant risk factors fol owed by sr and serum triglycerides Cholestero howev peared as a significant risk factor only in th age group in the total group As expected th nificance of age decreased as the age sp n groups became smaller Although the numbe small in the age group 40–49 years it is strikir how the role of BP disappears in this age interval On the other hand in the age group 50–59 years (not shown in Table V) BP had a very significant influence with *t* values around 6 Also the regression coefficients (*b* values) for systolic BP rose about 10-fold from the 40–49 to the 50–59 year group being e g in the prospective group 0 0020 and 0 0252 respectively Thus the role of systolic BP as a risk factor for IHD seems to become important only after the age of 50 years

In the stepwise multiple regression analysis (Table VI) age was the most important single in

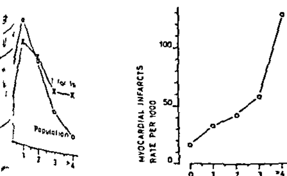


Fig 3 Prospective group *Left* Distribution of the total and the MI population by number of risk factors present *Right* Rate of MI in relation to number of risk factors present (top quintile for triglycerides cholesterol systolic BP Hb ESR and smoking)

Table IV *Rate of MI (per 1000) in relation to smoking physical activity position at work and education (prospective group all ages)*

	Low or no	Higher or yes	Highest
Smoking	20	56*	
Physical activity			
At work	37	47	51
At leisure	48	37	17
Position at work	39	42	41
Education	47	34	17*

All significances were tested against the low (no) group
*$p<0.05$ * $p<0.001$

dependent risk factor followed by systolic BP smoking plasma triglycerides ESR and Hb while plasma cholesterol did not appear as a significant independent risk factor either in the total or in the prospective group (Table VI)

The multiple logistic regression analysis with all 8 independent variables gave similar results (Table VII) with the same order of magnitude for the *t* values of the regression coefficients except that by this statistical method the coefficient for cholesterol was statistically significant

Plasma triglycerides and cholesterol as risk factors

To further analyse the role of triglycerides and cholesterol for the development of MI the study population has been divided into 4 groups on the basis of both plasma lipid levels as shown in Table VIII Three different arbitrarily chosen cut-off points for the upper normal limit for each plasma were used in this analysis

Regardless of cut-off poi s the g mal lipid levels always had the low IHD and the group with eleva of mixed hyperlipidaemia" had the higher remaining groups with either high ch high triglycerides were inbetween rate of new MI but had in most cantly higher values than the group *The high triglyceride group had* of IHD than the high cholesterol gro of the cut-off points used

Multiple risk factors

The effect of the increasing number of is shown in Fig 3 Only 18% of the tion had no risk factor 35% had one and 25% two risk factors Only 5% of the tion had four or more risk factors The farcts rose with the number of risk fact per 1000 in subjects without any risk almost 150 in those with 4 or more risk ten fold increase

DISCUSSION

The SPS does not comprise a random material of the Stockholm population caution must be exercised in generaliz results To evaluate any bias due to the morbidity of MI in the SPS was compar morbidity in the total Stockholm Coun tion 1 5 million for which a medical re system exists (1) which is based on all records and the cause-of-death regis tional *Bureau of Statistics* The expe quency corrected number of MI for the

Table V *Multiple logistic regression analysis with MI as dependent variable and 4 risk variables (t values for the regression coefficients and their significances are given)*

Age group (y)	*n*	Age	Systolic BP	Smoking	Tri-glycerides	Choles-terol
Total group						
40–69	2 512	9 0	7 9	5 9	3 6**	2 [illegible]
40–59	2 243	7 5	7 8	4 6	3 4 *	1 9
40–49	1 304	2 7	0 6	2 8	1 3	1 4
Prospective group						
40–69	2 326	7 2	5 5 *	4 7	2 0*	1 9
40–59	2 096	5 5 *	5 9* *	4 4	2 4 *	1 1
40–49	1 243	2 4	0 2	2 6	0 8	0 6

*$p<0.05$ **$p<0.01$ ** $p<0.001$

…Stepwise multiple regression analysis with MI as dependent variable (t values for the re… res… …fficients are given only when they were significant)

		Age	Systolic BP	Smoking	Triglycerides	ESR	Hb	Partial r value for cholesterol	Multiple R
	Rank[a]	1	2	3	5	4	6		
	t	9 6	5 1**	3 6	3 1**	3 8*	2 5	0 079	0 28
	Rank[a]	1	2	3	4	5	6		
	t	7 0 **	4 5***	3 6* *	2 6**	3 2	2 9	0 027	0 24
	Rank[a]	1	2	3		4	5		
	t	8 0 *	4 1**	4 1***	ns	3 2	2 8	0 030	0 24
	Rank[a]	1	3	2	5		4		
	t	6 2 *	3 4***	3 8***	2 6*	ns[c]	2 5	0 024	0 2

…stage the partial r value for triglycerides was 0 035
…s in which order in sequence the variable was entered into the multiple regression equation (see Methods)
…s variable was entered as number six into the regression equation it was not significant ($p>0$ 05)
… $p<0$ 01 $p<0$ 001

…as calculated from this register, was 30 9 …served number was 28 a non significant …ce (?) This indicates that the SPS popula… …s not biased in the sense that it had a dif… …morbidity of MI than the general population …holm.

…main reason for undertaking the SPS was to …e the individual role of plasma triglycerides …olesterol as risk factors for IHD in healthy …ecause we had at the end of the 1950s made …e observation that not only plasma choles… …ut also plasma triglycerides were raised in …rvivors (9) This finding has been confirmed …reat number of studies (3 4 7 16 22) …resent data confirm our preliminary finding …S (11) that elevated fasting plasma tri… …ides is a significant risk factor for IHD They …ubstantiate that patients with mixed hyper… lipidaemia are more prone to develop IHD th… those with either high plasma cholesterol alone …r high plasma triglycerides alone The figu…es … Table VIII also convincingly show that elevation of triglycerides alone is a significant risk factor and more so than elevation of cholesterol alone

The relatively greater importance of triglycerides than total plasma cholesterol is furthermore evident from the following facts (Table VIII) If the tri glyceride cut-off point is raised from 1 8 to 2 0 at a cholesterol of either 280 or 300 the morbidity of MI rises with 30 and 23% On the other hand if cholesterol is increased from 280 to 300 at a tri glyceride level of 1 8 or 2 0 the morbidity will either increase by only 5% or not at all

There is in general a positive correlation between plasma triglyceride levels and body weight (12 21) In SPS the r value for this correlation keeping age

…VII *Multiple logistic regression analysis with MI as dependent variable against 8 independent …les (t values for the regression coefficients are given)*

	Age	Systolic BP	Smoking	Triglycerides	Cholesterol	ESR	Hb	Weight/height index
…roup								
	10 3	8 2	5 8*	3 2**	2 7	4 4	3 7**	0 3
	8 4 *	7 9 **	4 8 *	3 2	2 6 *	3 1**	4 9 **	−1 7
…t group								
	8 3	6 6* *	4 6 **	1 8	2 6*	4 4 **	3 7	−1 5
	6 5*	6 0 *	4 0 *	2 5	2 3	2 3	4 5***	−1 9

… **$p<0$ 01 * $p<0$ 001

Table VIII *Rate of events (per 1000) of all categories of MI in relation to [illegible] cholesterol and triglycerides in men below 60 years of age in the prospective group*

% of population with normal lipids	Upper normal values		Lipid groups			
	Cholesterol (mg/100 ml)	Triglycerides (mmol/l)	Both normal	High cholesterol	High triglycerides	[illegible]
44	280	1 8	17	32	3[illegible]	[illegible]
47	280	2 0	18	32*	48	[illegible]
53	300	1 8	19	35	39	[illegible]
57	300	2 0	20	35	48	[illegible]
66	320	2 0	23	27	43*	[illegible]
74	320	2 5	24	34	45	6[illegible]

The statistical significance of differences was tested against the group with normal lipid values
* $p<0.05$ ** $p<0.01$ *** $p<0.001$

constant was 0 23 for men (12) Therefore considering the relation between plasma triglycerides and IHD it is of interest that the weight/height index was totally unrelated to the development of MI

The number of well documented cases of new MI was sufficiently high in this follow up to permit various kinds of multivariate analysis of the different risk factors The multiple logistic analysis including 8 independent variables showed that both triglycerides and cholesterol were independent risk factors with similar degree of statistical significance On the other hand when only five risk factors were introduced triglycerides appeared more strongly as a risk factor than cholesterol The more complex stepwise multiple regression analysis showed that when all variables were entered into the analysis six were significant independent risk factors for MI Here plasma triglycerides but not cholesterol appeared as a significant risk factor From the pure statistical point of view this analysis suggests that the role of cholesterol as a risk factor found in single factor analysis was not due to cholesterol itself but rather to the association between cholesterol and some of the other independent risk factors In fact cholesterol was significantly correlated to triglycerides age and ESR with *r* values of 0 35 0 13 and 0 14 respectively However the fact that cholesterol in this type of analysis did not show up as significant risk factor should not be interpreted to indicate that high plasma cholesterol was not a risk factor as great caution must be exercised in interpretations of multivariate regression analysis particularly when two or more variables are intercorrelated (17)

Furthermore the situation is extremely complex from the biochemical point of view [illegible] use of multivariate analysis for two [illegible] as plasma triglycerides and choles[illegible] cur together combined in fixed pro[illegible] plasma lipoprotein particles Let us f[illegible] take an increase of 0 5 mmol in plasma [illegible] This can occur by an increase in [illegible] of very low density lipoproteins (VLDL) [illegible] the most likely and/or in the num[illegible] density lipoproteins (LDL) An [illegible] mmol/l in VLDL triglycerides [illegible] VLDL cholesterol and conseq[illegible] cholesterol with 0 25 mmol because of [illegible] molar ratio cholesterol triglycerides of VLDL (10) If on the other hand the [illegible] triglycerides had been solely due to [illegible] the number of LDL particles the [illegible] figure would be a much higher [illegible] mmol/l in plasma cholesterol (10) Th[illegible] obligatory concomitant changes in pl[illegible] centrations of triglycerides and chol[illegible] magnitude and relationship of wh[illegible] upon which lipoprotein class(es) that [illegible] This raises very difficult problems in the [illegible] tation of statistical mul[illegible] plasma cholesterol and triglycerides The [illegible] is further complicated as changes in the [illegible] third major plasma lipoprotein class [illegible] density lipoproteins (HDL) [illegible] as changes in plasma choles[illegible] glycerides

There is a further complicat[illegible] pretation of statistical resul[illegible] plasma cholesterol conce[illegible] of HDL cholesterol appear to [illegible] (24) while high levels of LDL and VLDL

have the opposite effect This renders the l interpretation of statistical regression of rate of MI against total plasma choles te difficult as a rise in plasma cholesterol ve been due to either an increase in the HDL cholesterol or in the evil LDL or holesterol As an example of this com ne of the Framingham substudies com 815 subjects 49–82 years of age may be d (18) Not only total plasma cholesterol HDL cholesterol and plasma triglycerides easured in that study Although the ham study (20) was the first prospective show that total serum cholesterol is a risk r IHD in this particular substudy HDL rol was the major risk factor with an in sociation with the incidence of IHD while holesterol was not associated with the risk (18) Triglycerides were only associated in females

the role of plasma total cholesterol in spite omplexity as a risk factor for IHD has ocumented in most studies that of tri es has been controversial In a Finnish f 1648 middle aged men among whom 75 aths occurred during the seven year follow serum triglycerides and cholesterol were dent risk factors when analysed by multi analysis (26) In the multivariate analysis factors for IHD in the Göteborg study holesterol but not triglycerides emerged as pendent risk factor (29) The latter study ed however only 44 cases of IHD In ad to the biochemical reservations discussed both for the use of multiple regressions with cholesterol and triglycerides and for the use l plasma cholesterol there may of course regional differences in risk factors (23) may explain different results in risk factor s In fact when the mean values for plasma terol and triglycerides in SPS (12) and in the org study (29) are compared the triglyceride were 25% higher in Stockholm while the terol values were very similar Since plasma rides were determined in both places by ethod of Carlson this difference indicates a cant difference in populations between the wedish cities Such differences in population profiles may explain different outcomes with l to the relative importance of one or the other lipid as a risk factor for IHD The coopera tive lipoprotein phenotyping study (13) indeed showed great geographic variability in the relation of total cholesterol and triglycerides to the pre valence of IHD

It is interesting that both an elevated ESR and a high Hb value appear to be risk factors for MI and that the positive correlations are found even when age is eliminated through the calculation of par tial correlation coefficients An elevated ESR as a coronary risk factor was reported already in 1968 by Natvig et al (25) and Schiotz (27) and again by us in 1972 (11) A slight positive correla tion exists between the level of plasma lipids and the ESR values (5) but further studies of patients with asymptomatic hyperlipidaemia (6) showed that the most likely explanation is that the hyper lipidaemia causes silent vascular disease which in turn produces the ESR elevations The fact that patients who died from their first MI had signifi cantly higher ESR values than those who survived could be explained by more advanced vascular disease in the former A high Hb value was also found as a risk factor ESR and Hb values are strongly inversely correlated i e a low Hb con tributes to an elevated ESR Thus there could be no common cause for an elevated ESR and a high Hb value as risk factors for IHD Nor could the high Hb values and their effect on the IHD be explained as secondary effects of smoking as the positive correlation between MI and Hb values remained even when the effects of smoking had been elimi nated by means of multiple regression analysis It seems more likely that a high Hb value exerts a rheologic effect contributing to vascular damage and thrombosis

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Serum Ferritin during Inflammation A Study on Myocardial Infarction

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ACT The ferritin level in serum was investi t 9 patients with myocardial infarction all istory of chest pain of less than 4 hours before m. A significant rise in serum ferritin level nd in 8 patients The rise was generally smal that seen in acute infection and not signifi orrelated to the size of infarction as estimated anges in serum levels of myoglobin, ASAT H The rise started after a mean of 30 hours, k being reached within a week (M 4.3 days) erritin then fell to 120–300% (M 190) of the vel, where it remained An initial rise in ron levels was unexpectedly seen within 12 7 patients

rds serum ferritin serum iron inflammation ial infarction.

d Scand 206 361 1979

nflammation affects iron kinetics in several Hershko et al (14) and Beresford et al (2) hat the absorption of dietary iron fell during ation and a block in the release of iron e reticuloendothelial system (RES) cells to t has been found both in experimental in ation and infectious disease (13) Elevated levels in serum during infection and experi l inflammation have been found by several s (1 3 18 19 22 24 25) In previous longi l studies on patients with acute infections (4) ported serum ferritin elevations of long dura fter the infection had subsided It was found ferritin starts to rise within the first two days onset of fever and that the peak level is ed within a week in most patients It was sug d that the elevation of serum ferritin during in n is caused by an enhanced synthesis of fer rather than leakage from inflammatory cells e objectives of the present study were to in vestigate if an aseptic inflammation in vivo causes an elevation of serum ferritin and how soon after the onset of the inflammatory process this eleva tion if any starts Myocardial infarction was chosen as a model because it is known to cause an inflammatory reaction and because it is possible to define the starting point of the inflammation rather well since the dramatic onset of symptoms with central chest pain is easily recognized

PATIENTS AND METHODS

Patients Nine patients 7 men and 2 women 58–83 years old with clinically suspected myocardial infarction were selected for the study All had been admitted to hospital within four hours of onset of chest pain After a first examination at the Emergency Department the patients were transported to the Coronary Care Unit of the Department of Internal Medicine Test samples were collect ed every third hour during the first 24 hours and then every morning The observation time varied from 9 to 20 days (M 14) Abnormal myoglobinemia during the first two days was found in all patients (Table I) In five patients (nos 1–5) three other criteria of myocardial infarction were also fulfilled a history of central chest pain of at least 30 min duration increase in serum aspartate aminotransferase (ASAT) and development of ECG changes typical of transmural (4 cases) or subendocardial infarction (1 case) S-myoglobin was preferred to creatine kinase (CK) since recent investigations show that S-myoglobin is an indicator of myocardial damage just as early and sensitive as CK isoenzyme MB (28)

Cases 6 7 and 8 had abnormal myoglobinemia, elevated ASAT values and central chest pain for more than 30 min but unspecific ECG changes In case 9 the chest pain was left sided and varying only the first serum sample showed pathological ASAT value and the ECG was unspecific Two patients had a fatal reinfarction six months (case 1)

Abbreviations RES=reticuloendothelial system ASAT=aspartate aminotransferase ALAT=alanine aminotransferase LDH lactate dehydrogenase CK=creatine kinase

Table I Sc ne cl n cal a id l borat n d it i c i tle p it ents

Pat no	Sex	Age (y)	Durat on of pa n before adm ss on (h)	ECG	ASAT (µkat/l) on day 1	ASAT 2	ASAT 3	ALAT (µka l) on day 1	ALAT 2	ALAT 3	L [illegible] 1	[illegible]
1	♂	79	3	Anterior	0 8	7 7	1? ?	0 3	1 3	1 4	41	
?	♂	59	4	Subendocard al RBBB	0 9	1 0	0 5	0 3	0 4	0 4	44	1
3	♂	60	4	D aphragmat c lateral	0 8	7 ?	3 5	0 4	1 6	0 9	3	
4	♀	63	3	D aphragmat c	0 5	4 3	4 4	0 5	0 8	0 8	44	
5	♂	6	4	D aphragmat c	0 9	0 9	0 8	0 5	0 5	0 6		1
6	♂	83	3	Unspec f c ST T	1 3	0 9	0 4	0 7	0 5	0 4	41	11
7	♂	60	?	Left septal block	0 4	3 9	1 9	0 1	0 4	0 3	44	1
8	♂	64	3	LBBB	1 5	3 5	1 7	0 5	0 6	0 6		1
9	♀	58	3	Unspec f c T	0 9	0 3	0 3	0 3	0 3	0 3		1

and three months later (case 7) Case 5 comm tted su c de two months later and a healed myocard al infarct on was found at necropsy Case ? suffered a non fatal re nfarction four weeks later

Cases 1–6 were g ven i m inject ons of various analge s cs during the f rst ?4 hours in doses of max mally ? ml Further i m inject ons of analget cs were g ven to cases 3 and 6 during the second day and to case 1 also during the th rd day No other i m nject ons were g ven In case 4 an i v pacemaker system was implanted on day ?0 In case 6 cerebral symptoms of l doca ne intoxication were noted ?4 hours after adm ss on Cases ? and 7 were treated with i v nject ons of practolol during the f rst 1 ? days Serum samples were frozen unt l assayed The pat ents were followed up for 8–?0 days

Serum ferr n was measured by the rad o mmunoassay method of Wide and B rgegård (30) us ng l ver ferrit n labelled w th ¹²⁵I by conjugat on w th an iod nated pro p on c ac d ester accord ng to the princ ples of Bolton and Hunter (5) Results were expressed n arb trary un ts/l and the mean value for a group of 25 normal men was g en the value 100 arb U/l (range exp essed as 95% l m ts 40–?46) The reasons for us ng arb trary un ts were several there is no internat onal reference standard prep aration for ferrit n and consequently the normal range varies cons derably between laborator es We had no evi dence for the homogene ty of the ferrit n preparat on used Incidently our normal range corresponds well w th that g ven in µg/l by several well establ shed laboratories (9 16 ?9)

The inter plus intra assay variation calculated as the coeff c ent of variation from n ne repeated assays of con trol samples at three levels of ferrit n concentrat on was 8% for 19 arb U/l 6 5% f r 7? arb U/l and 4 4% for 180 arb U/l These three control samples are ncluded in every assay

Serum n was est mated rout nely in the Labora ory of Cl nical Chem stry by a Technicon Autoanalyzer The coefficient of variation was 4% w h n the normal range

Tran ferrin was measured by a nephelometric method accord ng to the princ ples of Lizana and He l ng (?0) The coeff cient of varia ion was 3% w h n the normal range

Enzymes ASAT ALAT and LDH were de term ned by the technique recommended by the [illegible] tee on Enzymes of the Scand na ian Soc e[illegible] Chem stry and Cl n cal Physiology The [illegible] variat on of the methods were 1 3 4 a[illegible] The upper l m ts of the refe ence ra[illegible] ASAT 0 6 ALAT 0 6 LDH ? 9

Ser m m glob n was mea ured by a [illegible] munoassay (?3) us ng myog obin labe [illegible] techn que descr bed by B[illegible] and H[illegible] reference value is 4? µg/l (range ?–[illegible] The [illegible] variat on of the method w h n the [illegible]

RESULTS

When the basal level (mean of the f[illegible] ferritin values) was compared w[illegible] 3 h ghest consecut ve values of each p[illegible] the 9 pat ents showed a s gn[illegible] serum ferrit n levels (Stud nt s t te[illegible]

Cases ? and 8 had pathol gical[illegible] tin levels already on adm ssion and ca[illegible] no rise (F g 1) In the others the m[illegible] from the in t al value was ?0[illegible] Of [illegible] normal b sal serum ferrit n level [illegible] above normal (patient 4 was a w[illegible] mal l m t f r women 180 arb U/l)

It was nvest gated how soon a s[illegible] t on of the b sal serum ferr n leve[illegible] samples were c llected every [illegible] f rst ?4 hours and a s[illegible] in th s t me in 4 pat en s After t e f[illegible] test samp es were co lected every [illegible] other 5 p t ents the n e in s[illegible] have started earl er than [illegible] mean value was 30 hours f[illegible]

g/l)	Hours from admission to peak level of myoglobin
peak level	
›100	9
515	6
1100	0
3600	6
870	3
5 0	12
5 700	9
1900	0
180	0

k serum ferritin concentration was reached 5 to 8 days (mean 3 8 days)

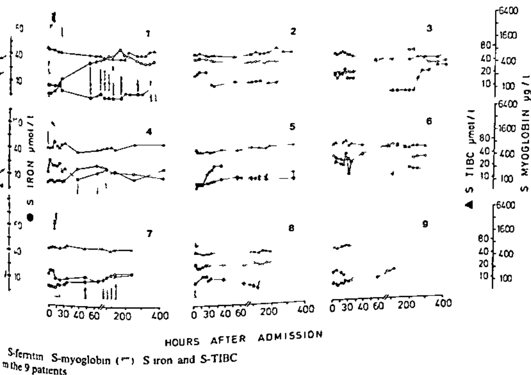
8 patients with a rise in serum ferritin only 6) returned to his initial level during the remaining at a level 70% higher than the vel (Table II) In 5 patients a plateau was 2-8 days (mean 4 8) after the day of the ue

y after admission a rise in serum iron of short duration was noted in 6 of the patients The peak was reached within 12 hours after admission in all but one (no 6) sho d another peak 24 hours later This initial pe d in no case be explained by the normal diurn ion in serum iron In 5 of the patients th n ensuing fall in serum iron to subnorm thin the next few days Patients 1 and 5 d no fall in serum iron had subnormal v mission

Transferrin n light changes during the study and the ried between the patients (Fig 1) No n was seen in this small series of patients betw the magnitude of serum ferritin peak (either in lute values or relative to the base level) and the myoglobin ASAT or LDH peak levels ASAT and myoglobin peak levels showed good correlation ($r=0.93$ $p<0.001$) There was no correlation between the number of days with fever and the magnitude of the ferritin peak

DISCUSSION

Elin et al (10) have shown that serum ferritin is slightly elevated in man in response to experimental inflammation induced by bacterial endotoxin and



S-ferritin S-myoglobin (—) S iron and S-TIBC in the 9 patients

Table II *Serum ferritin levels (arb U/l)*

Pat no	On admission (basal level)	Peak level	Final level	Difference peak level–basal level		Difference final level–basal level		Hours between onset of pain and significant ferritin elevation	[illegible]
				arb U/l	%	arb U/l	%		
1	80	565	270	485	600	190	238	16	[illegible]
2	380	412	350						
3	160	933	300	773	483	140	88	<49	[illegible]
4	80	213	122	133	166	42	52	<37	[illegible]
5	78	113	89	35	45	11	14	21	[illegible]
6	250	539	250	289	115	0	0	<33	[illegible]
7	80	174	170	94	118	90	113	24	[illegible]
8	270	357	350	87	32	80	30	[illegible]	[illegible]
9	75	156	95	81	108	20	27	21	[illegible]
Mean	161	382	222	247	208	72	70	<30	[illegible]

etiocholanolone The present work shows that this is true also for myocardial infarction It is notable that the elevations were much smaller than in acute infection (4) Two patients had an abnormally high serum ferritin level already on admission The reason for this is not known and they have not been investigated afterwards There was a small but significant rise in serum ferritin level ($p=0\ 0005$) in one of them and no rise in the other

The mean interval of 30 hours between onset of pain and the first significant elevation of serum ferritin level given in Table II is probably too long After the first 24 hours samples were not collected as frequently and there was a time lag of 9–24 hours between the 24 hour sample and the next The correct time is probably 24–30 hours This is in accordance with the results of Elin et al (10) who found that the rise in serum ferritin after experimental inflammation in man started after about 24 hours Just as in acute infection the peak serum ferritin was reached within a week in most patients (4) Several samples were taken from most of our patients before the ferritin elevation started which made it possible to define a basal level with some certainty in seven Serum ferritin did not return to its initial level except in one case At the end of the study it was 14–208% (mean 70) higher than initially In 5 patients a plateau was reached 2–8 days (mean 4 8) after the peak value The present study did not last long enough to answer the question whether the ferritin level actually returns to the basal level after some time

Experimental studies on acute infarction in dogs indicate that the peak levels of serum myoglobin strongly correlate with the histologic [illegible] (31) In large series of patients the [illegible] ASAT level correlates to the severity of [illegible] damage (7 8 15) and Hallgren et al [illegible] shown a correlation between serum AS[illegible] myoglobin peak levels in acute infarct[illegible] present study a correlation was found [illegible] serum ASAT and myoglobin peak levels [illegible] but not between these and ferritin peak [illegible] ($r<0\ 04$) Even if our series is very small [illegible] not seem likely that serum ferritin is [illegible] the size of the myocardial infarction [illegible] doubtful whether the elevated serum [illegible] caused by a release of ferritin from [illegible] myocardial cells Instead it could be [illegible] general enhancement of ferritin synthesis [illegible] has been proposed during infection [illegible] Iron is the natural stimulator of RES [illegible] thesis (32) and during inflammation [illegible] lated within the RES by several [illegible] block in the release of iron from the RES [illegible] been shown to exist during inflammation [illegible] and inflammation causes an [illegible] tion of injected ^{59}Fe in the ferritin of the [illegible] spleen in the rat (21) The question [illegible] elevated serum ferritin levels [illegible] myocardial cells or are the result of [illegible] synthesis may be elucidated by [illegible] munoreactivity of the serum ferritin [illegible] tional radioimmunoassay [illegible] ferritin and a radioimmunoassay [illegible] ritin which was however not [illegible]

A fall in serum iron was seen [illegible] days in 4 of our 9 patients [illegible]

gly enough there was an initial *rise* in n within the first 12 hours in 7 patients k coincides in time with the myoglobin d since myoglobin is an iron containing his could be suspected to cause the rise in on There is no correlation however be e magnitude of the myoglobin and serum s Furthermore myoglobin can carry only atoms per molecule and even if up to 5 000 myoglobin is released in some patients this it explain a rise in serum iron of up to 18 The ensuing fall in serum iron in most cases efore or at the same time as the elevation in rritin starts The suggested transport of n plasma into RES by lactoferrin proposed nick et al (26) could therefore theoretically portance for an acccumulation of iron with ES and an eventual stimulation of ferritin s

ACKNOWLEDGEMENT

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Clinical Features in Patients with Recurrent Myocardial Infarction

Runk Lofmark

From the Department of Med c ne Karol nska Inst tute at H dd n e Hosp tal H dd nge S eden

T A retrospect ve invest gation of 420 who had survived the acute phase of al infarct on revealed 63 reinfarctions (in 57 within three months Twenty eight patients out reinfarct on during the same period urvived three months without reinfarction arction patients were significantly more of n had more frequently a history of previous al infarct on and hypertension and their al infarctions were more often non trans- d localized to the anterior wall of the heart of each patient that was registered nearest the reinfarct on during hospitalization or discharge showed more often negative T

s recurrent myocardial nfarct on

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rtal ty during the first year after a CCU acute myocard al nfarction (AMI) is about Sweden (10) About two th rds of the deaths sed by an acute reinfarct on (19) Another ll susta n a non fatal reinfarction (6 17) l nical factors are known to pred ct a high leath after an AMI (4 1? 14 15 18) but on (16) present predictive data ident fying a at h gh risk of re nfarct on

study concerns the incidence of reinfarction onsecut ve series of CCU treated AMI pa and some characteristics of the pat ents who ed a recurrent AMI with n three months

PATIENTS AND METHODS

Pat ents w th AMI in tially treated n the Coronary nit CCU) at Huddinge Hosp tal 1972 76 4?0 were ged al ve from the CCU The d agnos s of AMI was 1) pro onged chest pain frank pulmonary or syncope and ?) appearance of an abnormal Q wave or R wave progress on and or a local d T vat on followed by a T wave invers on and o ra sed S-GOT values w th a max mum abc ut 4 ho onset of symptoms 4) f nd ngs at autop y o m infarct on at the stage correspond ng to the on e t toms S GOT was determ ned tw e daily during three days A 1? lead ECG (leads I II III aVF aVF CR4R CR CR CR CR and CR wa every morn ng for three days and then tw e weekl

The infarct was considered to be anterior f th changes were present in l ads CR lateral f in l aVL and/or CR and inferior if in leads II III and/o Transmural infarct on was cons dered when path Q-wave or R wave progress on appeared

The ECG of each pat ent that was reg stered p o t re nfarct on during the stay in hosp tal or prior to d charge was exam ned for Q wave changes R wave changes ST elevat on T wave nvers on ampl tude of the T wave and comb nat ons of Q- R ST and T wave changes

T waves cannot be evaluated properly in the presence of bundle branch block (BBB) preexc tat on (WPW) left ventricular hypertrophy (LVH) or atrial fibrillat on/flutter because these cond t ons affect the T waves appearance

The ECGs of the re nfarct on pat ents were compared w th those of the pat ents who survived three months w thout re nfarction The ECGs in the comparison were reg stered at the same number of days after the nfarct on

The study period extended over three months follow ng AMI Almost all surv vors were followed at the Outpat ent Department Re nfarct on was d agnosed by the same criteria as above

The s gnif cance of d fferences between mean values was tested by Student s *t* test The χ^2 test (w th Yates correct on) was used to test d fferences between relat ve numbers

RESULTS

Re f rct on

Of the 4?0 AMI patients d scharged al ve from the CCU ?8 d ed with n three months without proven

Abb ev at ons AMI acute myocard al infarct on CCU coronary care un t BBB bundle branch block WPW preexc tat on LVH left ventricular hypertrophy

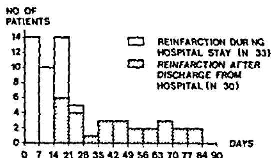


Fig 1 Interval between infarction and reinfarction

reinfarction (heart failure 14 sudden death <24 hours after onset of symptoms 8 cardiac rupture 2 other reasons 4) Autopsy was performed in 15 patients (57%) Another eight had been examined before death without suspicion of reinfarction In three patients neither a clinical nor a post mortem examination was performed

Fifty seven patients (12%) reinfarcted within three months four of them twice and one thrice Thus a total of 63 reinfarctions occurred (reinfarction group) the majority (68%) within four weeks and about half of them (48%) after discharge from hospital (Fig 1) Of the 57 reinfarction patients 16 (28%) died during the hospital stay and 15 (88%) were autopsied A total of 335 patients survived three months without reinfarction (survivors)

There was a significant predominance of women patients with previous myocardial infarction hypertension anterior and non transmural infarction among those who later reinfarcted (Table 1)

Postinfarction angina pectoris was registered in most of the patients during the hospital stay and the reinfarction group showed a tendency towards a higher frequency of angina (68% $n=50$) than the survivors without reinfarction (53% $n=312$)

The maxima of S-GOT for the primary infarctions and reinfarctions could be compared in 50 cases and no difference was found (157±84 and 135±74 U/l respectively $p>0.1$)

In 46 cases both the primary infarction and the reinfarction could be localized to a specific wall of the left ventricle (anterior lateral or inferior) One and the same wall was affected in both instances in 33 cases but not in 13 ($p>0.05$)

ECG

The ECGs registered prior to reinfarction during the stay in hospital or prior to discharge and the

Table 1 *Characteristics of ... and survivors with ...*

	[illegible]	[illegible]
Age (y)*	[illegible]	[illegible]
Women (%)	[illegible]	
Previous AMI (%)	[illegible]	
Previous angina pectoris (%)	[illegible]	
Diabetes mellitus (%)	[illegible]	
Hypertension (%)	[illegible]	
Medication on admission		
Digitalis (%)	[illegible]	
Quinidine (%)	[illegible]	
β blocking agents (%)	[illegible]	
Diuretics (%)	[illegible]	
Anterior AMI (%)	[illegible]	
Inferior AMI (%)	[illegible]	
Transmural AMI (%)	[illegible]	
S GOT max (U/l)*	[illegible]	[illegible]
ECG		
Showing atrial fibrillation/ flutter BBB WPW or LVH (%)	[illegible]	[illegible]
QRS frequency/min*	[illegible]	[illegible]
Medication after AMI		
Digitalis (%)	[illegible]	
Quinidine (%)	[illegible]	
β blocking agents (%)	[illegible]	
Diuretics (%)	[illegible]	[illegible]

* Mean+S D
*$p<0.05$ **$p<0.01$

time matched control ECGs were c... itative changes such as presence ... and R waves or ST segment eleva... differentiate the reinfarction group ... group

However when the study of the T ... interfered with by BBB LVH WPW ... lation/flutter a negative T wave ... more common in the reinfarction ... group (43/49 (88%) against 192/... Thirty nine (80%) and 161 ... had a QRS complex without ... the lead with negative T wave ...

DISCUSSION

Reinfarction is the most common ca... among patients who die after having ... acute phase of a myocardial infarction ... autopsy rate (92%) a fresh myoc... was found in two thirds of pa... two years after a myocardial infar...

dentifiable cause of death was found at
)

dictability of reinfarction would thus be nterest for the prevention of recurrence or a closer study of the course of pre n Many clinical factors known to pre lity after a myocardial infarction (1 3 5) have either not been tested or have to be ineffective as predictors of rein 8)

dy was confined to three months postin ainly because this period is important for on rehabilitation and a return to a normal reinfarctions also occur within these first 8) and the mortality from reinfarction de th time being about 50% in the first three d about 20% thereafter (9)

her series a reinfarction was more com tients with previous AMI or hypertension which probably explains why medication eptor blockers and diuretics was more n the reinfarction group The majority of it reinfarction patients sustained a non l primary AMI Such AMIs have previ n considered to have a better prognosis It has been observed that survivors of nural infarction have a higher long term gina pectoris recurrent infarction and ath than survivors of transmural infarc 70)

women in the present series more often l is not clear but a similar tendency has been presented (17) The primary infarc nore often localized anteriorly in the pa reinfarcted than in the controls The this is not obvious and similar findings een published

et al (16) have attempted to predict rein means of the ECG They observed that ine patients with recurrent postinfarction l simultaneous transient ST segment ele xperienced a recurrent AMI within six seventh patient reinfarcted within five

lacebo group of the Coronary Drug Pro correlation was found between negative in the ECG and mortality and sudden e months to three years following the not with reinfarction despite the fact that e mortality was attributed to coronary ase

Postinfarction angina was not systematically registered in this retrospective series so no conclusions can be drawn

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Effect of Plasma Free Fatty Acid Lowering on Exercise Tolerance and ST Segment Depression in Patients with Angina Pectoris

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The effect of a single oral dose of a lowering drug (5-(3-pyridyl) tetrazole) not act by conversion into nicotinic acid tolerance and ECG reaction was studied blind basis in 15 men with stable angina xercise was performed on a bicycle er the sitting position with a load increase m In addition to ECG, time to onset of and to termination of exercise because of l pains was recorded 5 (3 pyridyl) tet eased plasma FFA during exercise from µmol/l It reduced significantly the ST at corresponding work loads and permit tients to exercise 0 6 min longer, corre a 7% higher work load, before the onset un However absolute exercise time was cantly increased The most probable ex of the improved performance is a de nd and increased carbohydrate oxidation nemic heart, although a contribution may from hemodynamic effects of the drug, to effects on myocardial metabolism but volving heart rate and BP The lack of a t effect on performance time may have to general fatigue

plasma FFA angina pectoris exercise toler depression metabolic intervention
Scand 206 371 1979

nt to which different substrates are taken lized by the heart muscle is dependent on d concentration of the substrate in ques also on the blood concentration of alterna strates (19) Thus any change in plasma y acid (FFA) concentration would alter the and utilization of FFA but also in the direction the uptake of glucose (10 11 14 most situations plasma FFA is the predominant substrate of myocardial oxidative metabolism However for a given energy yield the combustion of lipids requires more oxygen than the combustion of carbohydrates as shown in animal experiments (13) and suggested by studies in man (18)

A procedure which increases the relative utilization of carbohydrates by the heart muscle would therefore offer a possibility to improve myocardial performance in patients with ischemic heart disease This might be achieved by drugs such as nicotinic acid which inhibit lipolysis in adipose tissue thereby lowering the plasma FFA concentration (1) Thus β pyridyl carbinol (Ronicol®) was found to reduce the extent of ischemic ECG changes in experimental coronary occlusion (9) In patients with angina pectoris nicotinic acid was shown to permit a higher angina threshold during atrial pacing (6) Luxton et al (12) on the other hand found a reduced ST segment depression during exercise but no effect on exercise tolerance by a nicotinic acid analog (5 fluoro 3 hydro-methylpyridinhydrochloride) in patients with stable angina pectoris The absence of effect on exercise tolerance is surprising if the effect on ST depression is to be taken as evidence of reduced oxygen deficit However nicotinic acid and its analogs have hemodynamic in addition to antilipolytic effects (11 17) which might obscure the implications of the results

The aim of the present study was to investigate the effect of 5 (3 pyridyl) tetrazole (P 5722) on exercise tolerance and exercise ST depression in patients with angina pectoris P 5722 is an antilipolytic drug with minimal hemodynamic effect (7) Our aim was to find out if any reduction of ST depression was parallelled by increased exercise

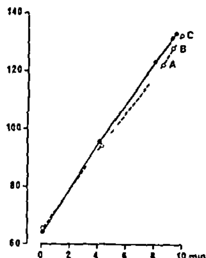


Fig 1 Heart rate at rest after 4 min exercise at the occurrence of chest pains (*A*) at the highest common load with and without P 5722 (*B*) and at termination of exercise because of chest pains (*C*) without and with P 5722

tolerance P 5722 unlike e g Ronicol®, exerts its effect without previous conversion to nicotinic acid In fact it is almost unchanged in the body and about 80% of the dose administered per os can be recovered in the urine

PATIENTS

men aged 33–66 years (mean 51) with stable pectoris since at least 3 months were studied Se of them had had a myocardial infarction more than year before the investigation All patients had horizontal or downward sloping ST depression of at least 1 5 mm in a left precordial lead during an exercise toler ance test (5) No patient had signs of heart incompensa tion neither did any of them have hypertension defined as systolic pressure above 160 and diastolic above 100 mmHg Four patients had been on β blocker and six pa tients on antilipolytic drug treatment However all drugs were withdrawn one month before the study

PROCEDURES

One month before the study the patients underwent an exercise tolerance test in the sitting position on a bicycle ergometer in which the load was increased by 10 W/min during continuous ECG recording The time at which chest pain occurred was noted and the test was discon tinued when intolerable chest pains had developed Each patient then performed two exercise tests on two consecu tive days after administration on a double blind basis of P 5722 or placebo On both occasions the patient reported to the laboratory at 8 00 a m after an overnight fast A short catheter was in[illegible] sampled for FFA determ[illegible] 5722 or placebo were given per os [illegible] the bicycle ergometer was [illegible] was increased by 10 W [illegible] selected so that intolerable pain [illegible] after about 8 min as judged from [illegible] was recorded before ($CR_{1\ 2\ 3\ 4\ 5\ 6}$) [illegible] (chest head leads from the same [illegible] for 10 min after exercise Sys[illegible] rest and systolic BP during exercise [illegible] the cuff method Venous blood for FFA [illegible] was taken at the end of exercise Plasma F[illegible] mated by the [illegible]Ni method (4) The ST le[illegible] CH_5) was taken to represent the ST le[illegible] leads P 5722 was provided by Dr C S[illegible] tral Research Sandwich Ker UK

Unless otherwise stated values for the [illegible] placebo groups are given as mean ± S E The [illegible] of differences between the groups [illegible] paired *t* test

RESULTS

Plasma FFA Basal plasma FFA was [illegible] placebo and 442±49 μmol/l in the P 5722 [illegible] the end of exercise it was [illegible] placebo which was not significantly [illegible] basal ($p>0\ 05$) while with P 5722 [illegible] to 299±38 μmol/l ($p<0\ 01$)

Exercise tolerance With placebo [illegible] curred after 7 9±0 9 min correspond[illegible] W and with P 5722 after 8 5±1 0 [illegible] ing to 120±11 W The difference was [illegible] nificant ($0\ 05<p<0\ 1$) Exercise was [illegible]

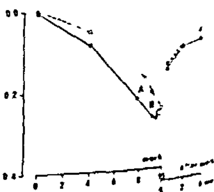


Fig 2 ST level in CH_5 at rest [illegible] occurrence of chest pains (*A*) at the [illegible] with and without P 5722 (*B*) at the [illegible] because of chest pains (*C*) and [illegible] after work without and with P 5722

ains after 9 4+0 9 m n w th placebo and 09 min w th P 5722 correspond ng to d 1 7+10 W respect vely The d ffer ot s gn f ant ($p>0\ 05$)

e (Fg 1) Heart rate at rest was 64±6 w h placebo and 67±5 with P 5722 In rela on to work load heart rate in gh y less w th P 5722 than w th placebo h ghest common work load it was 127+8 and 131+6 w th placebo ($p<0\ 05$) ts at the onset of chest pa ns and on n of exerc se d d not d ffer s gn ficantly 5722 and placebo

e at rest and during exercise d d not ficantly between P5722 and placebo At is 139/84 mmHg w th P 5722 and 137/85 th placebo on term nation of exerc se the essure was 140+4 and 142+4 mmHg ely However mmed ately after exerc se c pressu e was h gher w th than without 146+6 and 138+5 mmHg respectively while the d astol c pressure d d not d ffer Fg 2) At rest the ST level was zero w th and placebo In relat on to work load was depressed s gn f cantly less w th P n w th placebo and at the h ghest common was 2 1 mm and 2 7 mm respectively) At the onset of chest pa ns the level was m w h P 5722 and 2 2 mm w th placebo) and on term nat on of exerc se t d d not ween the s tuat ons be ng 2 55 mm and m respect vely ($p>0\ 05$) Over the first 10 exerc se the level d d not d ffer s gn f cant een P 5722 and placebo Occas onal ven p emature beats were recorded during n some pat ents w th no d fference be P5722 and placebo

DISCUSSION

p oduced a decrease n plasma FFA con tion during exerc se to sl ghtly more than half thout the drug The magn tude of the effect is to that found at rest wh ch was sim lar in tude although of sl ghtly shorter durat on than 300 mg n cot n c ac d per os (7) Most pa had a sl ght sk n flush wh ch means that the tration of the drug was not double bl nd in se sense However the flush and the vascular s n general are far less pronounced than those otinic ac d (7) Plasma FFA lowering would permit increased myocardial performance in pa t ents w th angina pectoris since it decreases the uptake and oxidat on of fatty ac ds thereby increas ing the utilization of carbohydrates (10) The ox da t on of carbohydrates yields more energy per un t oxygen than lip ds In accordance with th s it has been shown that the heart rate which can be ach eved by atrial pacing before chest pains occur is increased by nicotin c acid (6) However the extent to wh ch improved metabol sm is of pract cal im portance for the pat ent is probably better shown by exercise tolerance wh ch may be influenced also by hemodynam c effects of the drug

Thus Luxton et al (12) showed that a n cot n c acid analogue with but minor vascular effects de creased post exercise ST depress on in patients w th ang na pectoris However they d d not find any effect of the drug on exercise tolerance and ST depress on during exercise was not reported on If ST depress on m rrors myocard al schem a it is surprising that Luxton et al could not find any increase in exercise tolerance especially since both heart rate and BP during exercise factors of pri mary importance for myocard al oxygen consump t on were lower with the drug The influence on the exercise ECG or exercise tolerance may then have been due to other effects of the drug not related to those on l p d metabol sm The lack of s gn f cant effect on exerc se tolerance may also be expl uned by the fact that both the evaluat on of symptoms by the pat ent and the breaking po nt are rather subjec tive and factors such as general fat gue may well have contributed It is probable that the exercise protocol in the present study w th an almost con t nuous increase in load is more su table to define the time of appearance of symptoms as well as the breaking po nt (2) In the present study plasma FFA lowering bes des reducing ST depress on at cor responding loads increased performance time to onset of chest pa ns by 7% although the improve ment was barely s gn f cant The smaller d fference in absolute exercise time may as d scussed above be due to the add t on of general fatigue as a factor determ n ng the break ng po nt

The heart rate during exerc se was sl ghtly lower w th than without the drug Th s may have con tributed to the improvement in ECG and exercise tolerance by the treatment However although the systol c BP during exerc se was the same with as w thout the drug immed ately after work t was h gher with treatment It is therefore tempt ng to

conclude that the improved ECG reaction and exercise tolerance was the result of altered myocardial metabolism rather than an effect on the rate pressure product

It is not evident why the heart rate was lower with the drug since if a vasodilatory effect had remained at the time of exercise an increased heart rate would have been the more likely result It may have been the result of improved myocardial function with lower filling pressures (3) or less pain stimulation

ACKNOWLEDGEMENTS

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Late Sudden Death after Surgical Correction of Coarctation of the Aorta

Importance of Aneurysm of the Ascending Aorta

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ICT Follow up studies averaging 12 years ective surgery of 343 patients with coarcta ie aorta disclosed 38 late deaths, 16 of which lden unexpected and probably cardiovascu but two patients were normotensive post ely and in 4 of these the cause of death was dissecting aneurysm of ascending aorta In patient this aneurysm was repaired surgical i 3 other patients chest X ray had shown a iscending aorta before death At follow up nding aorta was dilated angiographically in 4 s who had moderate systolic hypertension tic valve disease The high incidence of n of ascending aorta in patients with coarcta probably due to hypertension during the eriod, possibly in combination with congeni ness of the aortic wall, and to concomitant he lesion

ls coarctation of the aorta aneurysm of the aorta late sudden death

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on the natural history of patients over 2 age with coarctation of the aorta have re n average age at death of 34–35 years (2 t review of 104 autopsied cases Reifen l (11) reported sudden death in 29 patients of whom 19 (18 3%) died from rupture/ n of the ascending aorta

era for patients with coarctation of the rted in 1945 when Crafoord and Nylin (4) d the surgical treatment However fol tudies after surgical correction have shown e is still a considerable incidence of sudden 10 13) The aims of the present work were the incidence and cause of late sudden er coarctectomy and to elucidate the role sm of the ascending aorta

PATIENTS AND METHODS

Between 1948 and July 1973 356 patients 129 females and 227 males underwent surgical correction of coarctation of the aorta in our hospital (12) Eighteen patients were in fants 120 1–12 years 154 13–29 years and 64 30 years of age or more There were 13 intra and postoperative deaths (3 7%) Ten of the dead patients were infants un der 5 months of age and the other three were 32 36 and 40 years of age A follow up study of all 343 survivors was performed in 1975–77 During the follow up period of 2–28 years (mean 12) 38 late deaths had occurred a review of these will be published elsewhere (8 14) Information concerning causes of death were obtained from family doctors hospitals where the patients had been admitted near relatives and the Norwegian Central Bureau of Statistics

The present study comprises primarily 16 patients who died suddenly and unexpectedly within one hour after onset of symptoms (4 7% of the 343 survivors) Death from cerebral vascular accident (5 patients of whom at least 3 died from subarachnoid hemorrhage) was not in cluded Four additional patients are included in whom aneurysm of ascending aorta was demonstrated at fol low up the aortography being performed because hyper tension was found Finally one patient is presented in whom aneurysm was found at the primary evaluation for coarctation of the aorta

RESULTS

The pertinent data on the 16 late sudden cardiovas cular deaths appear in Table I This part of the material was divided into 4 groups *Group I* Four patients who died from proven dissection/rupture of aneurysm of ascending aorta They were all normo tensive postoperatively and two had aortic valve disease Patient 3 was operated on for the dissection but he died on the 13th postoperative day In

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Table I *Data on 16 late deaths after coarctectomy (sudden unexpected death and [illegible] aneurysm of ascending aorta)*
AVD = Aortic valve disease AS = aortic stenosis AI = aortic insufficiency BAS = bicuspid aortic [illegible]

Group	Pat no	Sex	Age (y) At operation	Age (y) At death	Postoperative BP Years after operation	Postoperative BP mmHg	AVD
I	1	♂	9	27	8	130/80	-
	2	♂	15	18	3	135/75	AS AI
	3	♂	17	30	12	130/90	AI
	4	♂	19	25	3	115/80	-
II	5	♂	22	42	12	140/90	BAS AI
III	6	♂	15	23	<1	130/80	-
	7	♂	33	43	1	170/75	-
	8	♂	48	58	9	170/100	-
IV	9	♂	6	17	1	95/70	-
	10	♂	13	14	1	130/80	AI
	11	♂	16	23	6	155/90	-
	12	♂	24	25	-	-	-
	13	♀	30	45	2	170/100	-
	14	♂	31	47	2	150/80	-
	15	♂	36	45	6	135/80	-
	16	♂	50	54	-	-	AI

patients 1 and 4 the aneurysm had ruptured into the pericardium Histological examination of the ascending aorta was obtained from two patients (nos 3 and 4) and in both the media was thin with disruption of the few elastic fibres *Group II* One patient who had bicuspid aortic valve with insufficiency requiring valve replacement 12 years after coarc[illegible] y In conjunction with the aortic valve sur[illegible] y an aneurysm of ascending aorta was repaired with a graft *Group III* Three patients who died suddenly and unexpectedly All had before coarctectomy shown dilatation of the ascending aorta on chest X ray giving a clue to rupture of the aorta as the cause of death *Group IV* Eight patients who all died suddenly and there were no clues to the causes of death Only one of them (no 9 [illegible] and the sole pathological finding was [illegible] ventricle There was no significant [illegible] site of coarctation In two patients [illegible] diastolic murmur was present [illegible] ing aortic insufficiency Modera[illegible] found in one patient whereas [illegible] were almost normotensive

The mean interval from the [illegible] death was 10 years (range 1-20) and [illegible] under 40 years of age at death 35 [illegible] males The incidence of sudden [illegible] operated on after 13 years of age was [illegible] the younger patients 1 6[illegible]

At follow up of the survivors [illegible]

Table II *Data on 4 patients with aneurysm in ascending aorta detected at f[illegible]*
AVD = aortic valve disease R = resection DG = dacron graft ETEA = end to-end anas[illegible] ER = [illegible]
BAS = bicuspid aortic valve AI + = small aortic insufficiency AI + + + = large aortic insufficiency

Pat no	Sex	Age (y) At operation	Age (y) At follow up	Operative technique	BP at follow up (mmHg)	Recoarctation press grad (mmHg)	AVD
17	♂	14	23	R DG ETEA	175/90	60	BAS [illegible]
18	♂	14	23	R ETEA	155/100	40	BAS
19	♂	16	31	R ETEA	180/90	36	BAS [illegible]
20	♀	29	35	ER	160/90	14	BAS [illegible]



...ortography from patient 18 showing dilated as... ...rta and a saccular aneurysm just below the left ...artery

...ing aorta was found in four (Table II) They ...icuspid valves and three (nos 17 19 and ...) aortic insufficiency Patient 20 had been ...lly treated for bacterial endocarditis 13 ...fter coarctectomy A significant recoarcta... ...s present in patients 17 19 In patient 18 a ...calcified saccular aortic aneurysm with a ...t of 3 cm was found just distal to the site of ...tion (Fig 1) Fig 2 shows the aneurysm of ...ending aorta in patient 20

... shows the dilatation of the ascending aorta ...-year-old man who recently underwent pri... ...evaluat on for coarctation BP was 170/100 ... the pressure gradient across the coarctation ...Hg and the aortic valve was bicuspid with ...ufficiency or stenosis

DISCUSSION

...present finding of a high prevalence of ...ysm of ascending aorta after surgical correc... ...coarctat on of the aorta is remarkable as ...few such cases have been reported previous... ...6 7 10 15 16) Most of the present patients ...normotensive postoperatively and a clinical ...nation just prior to death would probably not have predicted rupture of the aneurysm or sudden death from other causes However signs of aortic valve disease were present in 5 of the 16 patients The present study has also shown a considerable overall incidence of late sudden death after co arctectomy 4 7% during follow up periods of 12 years on average This is in good agreement with the report of Maron et al (10) A follow up after 11–25 years of 194 patients revealed 23 (12%) late deaths 22 of which were related to cardiovascular disease the mean age at death was 35 1 years Autopsy was performed in eight of the cases and rupture of aortic aneurysm was found in two Death was sudden and unexpected in 11 of the 14 patients not autopsied Ruptured major arterial vessel was probable in four of these patients and myocardial infarction in two others In this material non sur vivors had experienced significantly longer periods of preoperative hypertension than survivors

Simon and Zloto (13) studied 190 patients 1–15 5 years (mean 6 6) after operation There were 11 late cardiovascular deaths the mean age at death being 32 5 years Five patients died suddenly and autopsy



Fig 2 Aortography from pat ent 20 showing aneurysm of the ascending aorta



Fig. 3. Dilatation of the ascending aorta in a 19 year-old man with unoperated coarctation of the aorta

was performed in only two. Dissecting aortic aneurysm was found in one.

In their classical review, Reifenstein et al. (11) [illegible]rted dissection of the ascending aorta in 18.3% [illegible] patients dying with the coarctation, their mean [illegible] being 30 years. It is therefore not surprising that some of the preformed aneurysms in the course of time will rupture even after normalization of the BP by coarctectomy.

Broden and Karnell (1) studied 123 cases by aortography before coarctectomy and frequently found dilatation of the ascending aorta, the dilatation sometimes being so severe that the vessel was saccular. They also made a comparison between the mean width of the ascending aorta in coarctation and the corresponding values in normal cases. The results indicated that in coarctation the ascending aorta was wider than normal even in the first decade of life and that this difference increased with age. The cause of the dilatation of the ascending aorta in patients with coarctation is not yet clarified. Congenital thinning and medial changes due to hypertension or other factors have been discussed (11). However, hypertension during the growth period is probably of great [illegible] but a contribution from congenital weak[illegible] aortic wall cannot be excluded. [illegible] microscopic studies can solve th[illegible] histological findings in [illegible] accordance with the findings [illegible] ported by White et al. (16) indica[illegible] pathogenesis. The con[illegible] may also be of importance in th[illegible] phasized by Edwards (6) aortic [illegible] to bicuspid aortic valves may lead [illegible] laceration of the ascending aorta [illegible] may lead to classical dissecting aneur[illegible] localized saccular aneurysm.

The incidence of sudden dea[illegible] in patients operated on after puberty [illegible] dren. This finding might be due to the [illegible] the hypertensive stress on the aorta [illegible] shorter the younger the patients [illegible] omy. On the other hand, only a few [illegible] followed more than 20–25 years after [illegible] in childhood.

The present follow-up study led to [illegible] of aortic aneurysms in 4 patients [illegible] mainly systolic hypertension. [illegible] had a[illegible] disease, and 3 had recoarctation with a [illegible] gradient of 40 mmHg or more. In these [illegible] lesion of the aortic wall may have [illegible] formation of aneurysm. Frederiksen et al. [illegible] have described spindle-shaped d[illegible] ascending aorta in 8 out of 37 patients [illegible] went aortography after coarctectomy. [illegible] was interpreted as a sign of [illegible] pressure gradients were not measured. [illegible] series of postoperative aortography [illegible] ported in the literature.

Pregnancy in women with unopera[illegible] of the aorta implies a risk of ma[illegible] main danger is dissection of the as[illegible] This danger will probably [illegible] tomy in women with aneurysm of [illegible] aorta.

As previously emphasized by [illegible] there is a need for close [illegible] after surgical correction of coarctation [illegible] Aortic valve disease may progress and [illegible] times lead to laceration of the ascending [illegible] Overall, there is a considerable risk [illegible] aortic aneurysm some years after surgery [illegible] is highest in patients with [illegible] sion, even moderate [illegible] hypertension

...ll for surgery in childhood using a thorough ...le technique and leaving no residual pres... ...ent at the site of coarctation

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Oesophageal Symptoms and Manometry in Valvular Heart Disease

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CT A possible relationship between heart
oesophageal dysfunction (OD) and symp-
, was studied in 47 patients with valvular
ase They were investigated with oesoph-
ometry and oesophageal acid perfusion
was found in 32% of the patients. A local
crease in the middle part of the oesoph-
bably an effect of cardiac enlargement and
on of the oesophagus was found at ma-
n 38%. The incidence of OD and of oesoph-
ptoms was the same in patients with and
oesophageal compression. We did not find
tions that valvular disease in itself provokes
that symptoms of chest pain and cough in
with valvular heart disease are due to OD

oesophageal function valvular heart disease
Scand 206 381 1979

previously found a high incidence of
geal dysfunction (OD) in patients with
d or proven coronary heart disease (8 9)
patients observed in a coronary care unit
of chest pain (2) Our survey of the inter
hip between OD and heart disease is con-
ere with data on patients with valvular heart

symptoms of valvular heart disease vary
type and severity of the lesion Two of the
s may be chest pain and cough Since both
mon in patients with OD (2 10) symptoms
nd in valvular heart disease could be due to
condary to mechanical influence of the en-
heart on the oesophagus The aim was there
investigate the incidence of OD in a group of
with a well defined chronic valvular heart

PATIENTS AND METHODS

The study comprises 26 male (mean age 53.? years, range 3? ?1) and 21 female patients (mean age 53.6 years, range 43-69) referred to the Cardiology Unit for preoperative heart catheterization. Twenty-three patients had aortic, 9 mitral and 15 both aortic and mitral valvular disease. Six of the patients were classified as belonging to function group I according to the NYHA, 19 to group II and 22 to group III.

Besides the cardiac investigations which included right and left heart catheterization, left ventricular angiography and thoracic aortography, an oesophageal manometry and an oesophageal acid perfusion test were performed. The patients also filled in a questionnaire regarding symptoms of possible oesophageal or cardiac origin (6 7). Oesophageal symptoms such as globus sensation, dysphagia and chest pain were given point scores and an oesophageal symptom score was calculated for each patient. The symptom score was slightly modified after Spandow et al (7).

Sphincter tonus, sphincter displacement, gastro-oesophageal reflux, oesophageal tonus and motility by swallowing were investigated at the oesophageal manometry (7). The acid perfusion test was slightly modified from the original Bernstein test (1 3).

OD was considered to be present if at least one of the following criteria was met. 1) Positive acid perfusion test. 2) Manometrically verified hiatal hernia with a length of 2 cm or more. 3) Dysmotility in combination with hypotension of the lower oesophageal sphincter (LES) or reflux. 4) Severe dysmotility, i.e. segmental contractions by swallows at 3 or more of 10 different levels in the oesophagus. Hypotension of the LES or gastro-oesophageal reflux as a single finding or a local pressure increase in the middle part of the oesophagus were not classified as OD.

Heart volume was calculated according to Jonsell (4) from chest X-rays taken in the standing position.

Fisher's exact test, Wilcoxon's rank sum test and Student's *t* test for unpaired data were used for statistical analysis.

Abbreviations OD=oesophageal ... lower oesophageal sphincter

Table I. *Outcome of oesophageal function tests*
M = mitral valvular disease. A = aortic valvular disease

	M (n = 9)	A (n = 23)	M + A (n = 15)
Hernia	0	5	2
Dysmotility	4	5	4
LES incompetence	5	11	3
Positive acid perfusion test	1	3	4
OD	3	7	5

RESULTS

OD was found in 32% of the patients (Table I). The incidence of OD did not differ between the three groups of valvular disease. The patients with OD had an increased frequency of heart burn, acid regurgitation, globus sensation and surfeitness after meals (Table II). A history of chest pain was presented by 62% of the patients and 36% complained of cough, but the difference in incidence between patients with or without OD was insignificant. The rank sum of oesophagus related symptoms was 478 for the 15 patients with OD and 701 for the 32 with normal oesophageal function ($p<0.01$). Patients with aortic valvular disease alone had more often chest pain (74%) than patients with mitral valvular disease alone (22%) ($p<0.02$). All patients who presented typical effort angina at the time [illegible] aortic valvular disease.

Table II. *Symptoms given in the oesophageal questionnaire in relation to objective findings in 15 with and 32 without OD*

	OD (%)	Non-OD (%)
Do you often have heart burn?	13	0
Do you often have acid regurgitations?	33	9
Do you often feel a lump in your throat?	33	13
Do you often feel surfeited after a meal?	40	13
Do you often have a hacking cough?	40	34
Do you sometimes have chest pain?	67	59
Does your chest pain improve when lying with your head raised?	27	25
Do you sometimes wake up at night because of chest pain?	33	25
Do you sometimes get chest pain in cold environments?	20	44
Do you get chest pain with emotional distress?	33	53
Does your chest pain get worse in connection with effort?	67	56
Effort angina at exercise test	13	9

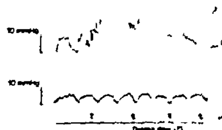


Fig. 1. Pressure registration from the [illegible] oesophagus in a patient with [illegible] valvular disease (upper) and in a [illegible] disease (lower). The sinusoidal [illegible] lower registration is due to [illegible]

A local pressure increase of [illegible] (range 3–15) in the middle part of the [illegible] was found at manometry in 38% [illegible] tients. The mean length of the [illegible] increase was 5.3 cm and its lower [illegible] average 6.5 cm above the LES. [illegible] sure increase, pressure variations [illegible] were sometimes superimposed on the [illegible] trations (Fig. 1). These pressure [illegible] bled atrial pressure variations and [illegible] patients with sinus rhythm and [illegible] with atrial fibrillation.

There was no difference in [illegible] tween the group of patients with [illegible] crease (5/18) and the group [illegible] (10/29). Neither was there any [illegible] ageally related symptoms between the [illegible] There was no overrepresentation of [illegible] mitral stenosis or mitral regurgitation [illegible] with local pressure increase in the [illegible] mean roentgenological heart volume [illegible] (S.E.M.) ml/m BSA for the group [illegible] sure increase and 656±32 for the [illegible] ($p>0.05$).

DISCUSSION

An increase in pressure [illegible] the [illegible] observed in more than one third of our [illegible] There was no relation between heart [illegible] ray and pressure increase [illegible] etry, in accordance with [illegible] helmsen (11). This is partly [illegible] that X-ray pictures do not allow [illegible] the size of separate heart chambers [illegible] patients with [illegible]

d to have enlarged left atria there was no representation of local pressure increase in the ...gus Therefore other factors such as the ...ation of thoracic spine and the cardiac/ ...antero-posterior distance ratio may be of ...ce but were not evaluated here

...ugh the observed pressure increase within ...ophagus is low compared to the magnitude ...ressure increase induced by swallowing it ...ve rise to OD and oesophageal symptoms ...e previously found that more than 50% of ...s with chest pain have signs of OD (7 8 9) ...schel and Paulsen (10) reported that one ...f their patients with hiatal hernia or reflux ...s of bronchitis Among our patients 62% ...st pain and 36% cough The question there ...ses if chest pain and cough in patients with ...r heart disease are due to an overrepresenta- ...OD provoked by cardia enlargement The ...ce of OD however was only 32% among ...ents and the frequency of chest pain or ...d not differ significantly between those ...d without OD Therefore it does not seem ...at symptoms of chest pain and cough in ...s with valvular heart disease are caused by ...r did we find any indications that a valvular ...with cardiac enlargement provokes OD ...e incidence of OD was similar in patients ...d without local pressure increase in the ...gus

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Disopyramide Plasma Levels in Cardiac Patients on Maintenance Therapy

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CT The antiarrhythmic agent disopyra a dosage of 200 mg/8 h was given to 7 car ents. The drug was fairly rapidly absorbed ean peak plasma concentration (3.5 μg/ml) ared 1 h after administration of the first ean biological half life (7.8 h) was slightly l compared to that reported in normal vol bjects. Mean steady state plasma concentra in the therapeutic range were attained 24 the start of medication The fluctuations in a levels were in the order of 30 % however, read of the values was observed The drug lerated

d sopyramide card ac pat ents absorption dosage interval.

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mide (4-d sopropylamino-2 phenyl 2 (2 utyramide) is pharmacologically related to hmic drugs such as quinid ne and pro- The drug reduces the incidence of ven d to a lesser extent atrial arrhythmias (4 3) and it has been shown to be a safe and agent in the prevention of potentially seri thmias following myocardial infarction (9 drug is also effective in maintaining sinus patients after electroconversion of atrial n (6)

levels between 2 and 4 (5) μg/ml are o be required for optimal antiarrhythmic 13 14) Deano et al (4) have demon at an i v bolus of 2 mg kg of disopyramide followed by continuous i v drip infusion h caused a marked reduction in frequency cular premature contractions This effect ed to serum levels of approximately 2 5-

Side-effects of disopyramide are primarily related to its anticholinergic action and they consist mainly of dry mouth blurred vision and in patients with hypertrophy of the prostate urinary hesitancy may occur (8 14)

Cardiac and renal failure may influence the absorption distribution metabolism and elimination of several cardioactive drugs including disopyramide (2 15 17 18) and delay the attainment of steady state plasma concentration (C_{ss}) Adjustment of the dose accord ng to the plasma concentration will however allow optimal treatment of patients with renal failure or low cardiac output states In the present study we have measured steady state levels of disopyramide in cardiac pat ents and present further clin cal evidence that adequate maintenance therapy is possible at a fixed dosage interval slightly longer than that recommended to healthy human volunteers (18)

PATIENTS AND METHODS

Seven pat ents w th heart d sease participated n the study Informed consent had been obta ned from all The r age diagnos s physical characterist cs and haemodynam c parameters are shown in Table 1 Cl nical and haematological exam nat on revealed otherwise no abnormalit es The renal funct on wh ch was assessed by serum creatin ne measurements was sl ghtly impa red in pat ent 2 (170 μmol/l) Most of the pat ents were subjected to cont nuous ECG mon tor ng in a coronary care un t throughout the invest gat on period S x pat ents had ventricular premature contract ons not requ r ng adequ te antiarrhythmic therapy one pat ent had paroxysmal atr al fibrillation A left heart catheterizat on with ventr cular and select ve coronary ang ography was perf rmed in 5 pat ents

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Abbrev at ns $t_{½}$ = biological half l fe F = el m nat on rate constant ECG = electr card ographic C_{ss} = ste dy state plasma concentration

Table I *Details of the patients*

LVEDP = end diastolic pressure of the left ventricle CM = cardiomyopathy MI = myocardial inf[illegible] VPC = [illegible]lar premature contractions PAF = paroxysmal atrial fibrillation LV = left ventricle (ventricular)

Pat no	Age (y)	Sex	Diagnosis	Arthythmia	Heart size (rel volume)	LVEDP (mmHg)	Digitalis	Angiography
1	34	♂	CM	VPC	545	14	+	Red[illegible] LV [illegible] arteries
2	63	♂	MI	VPC	420	11	+	LV dyskinesia [illegible] artery [illegible]
3	48	♂	MI	VPC	460	13	–	LV an[illegible] [illegible] artery [illegible]
4	58	♂	MI	VPC	625	25	+	LV dyskinesia [illegible] fraction [illegible] arteriogram
5	78	♀	MI	VPC	630		+	
6	50	♂	MI	VPC	390	18	–	LV [illegible] aneurysm [illegible] stenosis
7	67	♀	MI	PAF	440		+	

Table II *Individual and mean plasma concentrations of disopyramide (µg/ml)*

Pat no	Disopyramide 200 mg[1]	Hours after the start of disopyramide medication ½	1	2	4	6	8	Disopyramide 200 mg	9	10	[illegible]
1		0.4	2.4	3.2	2.5	2.2	1.7		1.7	[illegible]	[illegible]
2		0	3.6	2.7	2.8	2.1	[illegible]		1.8	[illegible]	[illegible]
3		1.9	4.7	4.3	3.9	3.2	[illegible]		3.2	[illegible]	[illegible]
4			[illegible]	2.3	1.5	1.3	1.3		[illegible]	[illegible]	[illegible]
5							1.8		2.5	[illegible]	[illegible]
6		4.4	5.4	5.1	3.4		2.1		4.0	[illegible]	[illegible]
7		0.5	2.3	2.9	2.5	2.1	2.2		[illegible]	[illegible]	[illegible]
Mean		1.8	3.5	3.4	2.8	2.2	2.0		[illegible]	[illegible]	[illegible]
± S D		2.1	1.3	1.1	0.8	0.7	0.5		0.8	[illegible]	[illegible]

[1] First dose given at 8 a m

Drug administration schedule

Disopyramide (Durbis®) 200 mg was given at 8-hour intervals initially at 7 a m in the fasting state and then at 8 16 24 32 40 48 56 64 and 72 h after the start of the investigation

Blood samples and disopyramide assay

Blood samples (10 ml into lithium heparin anticoagulant) were drawn through an indwelling Venflon cannula inserted into an antecubital vein at 30 min and at 1 2 4 6 8 9 10 12 14 24 25 26 32 33 34 48 50 72 and 74 h after the first dose After centrifugation plasma was stored at −20°C in plastic tubes until analysed Estimation of the plasma concentration of disopyramide was carried out at the Roussel Laboratories Swindon by a gas liquid chromatographic method using a 3% OV 1 column (5)

Table III *[illegible]*

Pat no	$t_{½}$ (h)	k_{el} [illegible]
1	[illegible]	[illegible]
2	9.0	[illegible]
3	[illegible]	[illegible]
4	5.0	[illegible]
5		[illegible]
6	6.0	[illegible]
7	[illegible]	[illegible]
Mean	[illegible]	[illegible]
S D	1.9	[illegible]

I\ Ind dual and mean plasma concentratıons of d sop\ramıde (μg/ml)

Disopyramide 200 mg	Hours after the start of d sopyram de med cat on: 24	25	26	D sopyram de 200 mg	32	33	34	D ff between max and m n values (%)
	2 4	2 4	3 0		2 4	7 5	3 4	4?
	3 6	7 ?	9 1		4 0	5 0	5 5	38
	3 0	6 9	5.3			2 ?	4 0	
		1 7	3 9		1 9	3 6	1 3	30
	3 ?	3 3			3 2	3 1	4 5	40
	2 3	3 8	4 5		?6	2 7	3 6	38
	2 7	?9	3 7		2 4	3 5	3 8	58
	2 9	4 0	4 9		?8	3 ?	3 7	31
	0 5	2 2	2 2		0 7	0 9	1 3	31

RESULTS

[Disopy]ramide gi en at 7 a m on the first day was [absorbe]d ran dly and the h ghest mean plasma con[centrati]on (3.5+1 3 μg/ml) was measured 1 h after [administ]ra on (Table II) The drug was elim nated [from th]e blood w th a mean b olog cal half life ($t_{½}$) [of] 6 9 h (range 5–9 5) (Table III) The ind [ividual] values were derived from the sem log [arithmic] p asma concentrations vs time plots [after th]e first dose (Table III) The mean el m [ination] ra e constant (k) was 0 095+0 077 h [(range] 0 138–0 073) (Table III) The second [dose] admin s ered at 3 p m (approximately 1 5 [h after] intake of food) produced a lesser increase [in the m]ean plasma concentrat on and the drug [was el]imina ed at a slower rate (Table II) The [minimu]m p asma concentration was defined as the [lowest] concentrat on of d sopyram de at each dose [interv]al 4–3? h after adm n strat on of the first dose the mean m n mum plasma concentration was approximately 3 μg/ml and rema ned at that level throughout the rest of the study (Tables IV and V) The mean d fference between the minimum and maximum plasma concentrations (determ ned 2 h after intake of d sopyram de) was approximately 30% at steady state plasma levels however there was a w de spread of the values observed (Tables IV and V)

The drug caused sl ght ant chol nerg c effects in some patients but was otherwise well tolerated

DISCUSSION

This study demonstrates that disopyram de given to cardiac patients in fasting state was absorbed fairly rapidly from the gastro ntestinal tract and peak plasma levels assumed to be with n the therapeut c range were attained 1 2 h in all and mainta ned

V Ind dual and mean plasma concentrations of disop\ram de (μg/ml)

Disopyram de 200 mg	Hours after the start of d sopyram de med cat on: 48	50	Diff between max and min values (%)	D sopyram de 200 mg	72	74	D ff between max and m n values (%)
	2 1				2 2		
	4 6				4 7		
	3 8	4 9	30		4 4	5 0	14
	3 5	5 3	51		4 1	4 8	17
	2 1	2 0	5		2 2	3 0	37
	3 0	4 6	53		2 9	4 0	38
	2 6	3 0	15		2 3	3 9	70
	3 1	4 0	29		3 2	4 1	35
	0 9	1 4	25		1 1	0 8	2.

in most patients for at least 8 h after the first dose. The peak plasma concentrations correspond well to those found by Whiting and Miller (18) in healthy volunteers. On the other hand, the values are considerably higher than those observed by others in normal subjects (3). Ward and Kinghorn (17) found that the most striking difference between patients and healthy volunteers after identical oral doses was the much lower plasma concentration profile observed in the former. In patients with heart failure, the absorption of quinidine and procainamide is often delayed (1, 12). The reason for these discrepancies is not obvious. The reduced and apparently delayed absorption—and the slower elimination associated with the second dosage (given 8 h after the start of the medication)—is probably related to intake of food which delays gastric emptying. Disopyramide is a weak base (pK_a 9.2), and the absorption will therefore take place in the gut.

Disopyramide is predominantly (40–60% of the dose) eliminated by renal excretion of the unchanged drug, 15–20% as the mono-N-dealkylated metabolite (11). It has been shown that $t_{\frac{1}{2}}$ was not appreciably affected down to a creatinine clearance of 60 ml/min^{-1}. The mean $t_{\frac{1}{2}}$ of 7.8 h and the mean k_{el} of 0.095 h^{-1} found in this investigation are in accordance with values previously found in cardiac patients (15, 17). In healthy volunteers, the reported values for $t_{\frac{1}{2}}$ and k_{el} were within the ranges of 4.4–6.0 h and 0.110–0.173 h^{-1}, respectively (11, 15, 18). The altered elimination characteristics for disopyramide observed in cardiac patients may be related to impaired hepatic metabolism and/or reduced renal excretion secondary to cardiac failure (2).

When a drug is administered orally, the desired C_{ss} is achieved after 4–5 × $t_{\frac{1}{2}}$. In the present study, a mean C_{ss} within the therapeutic range was attained 24–32 h after the start of medication. The mean fluctuations in the C_{ss} were in the order of approximately 30%.

In healthy volunteers, Whiting and Miller (18) have assumed that substitution of relevant mean kinetic parameters into the formula of Wagner et al. (16) and a C_{ss} of 3.5 μg/ml would necessitate an oral dose of 200 mg/6 h.

$$\text{Dose} = \frac{k_{el} \times V_D \times T \times C_{ss}}{f}$$

where V_D = volume of distribution, T = dose interval, f = bioavailability.

In most of our patients k_{el} was [illegible] probably reduced (15, 17); hence the dosage interval had to be increased. In patients with heart failure associated with low [illegible] states, recommendations for dosage [illegible] cannot be derived from normal [illegible]. Close monitoring of plasma [illegible] concentrations will, however, allow an [illegible] adjustment to be made and is therefore [illegible].

Except for slight symptoms [illegible] anticholinergic effect of disopyramide [illegible] well tolerated by our patients.

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Reduced Vibratory Perception and Corneal Sensitivity and Metabolic Disturbances Following Intestinal Bypass Surgery

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ACT Decreased corneal sensitivity and n perception suggesting a diagnosis of ropathy were demonstrated in some of 26 who had undergone intestinal bypass Psychological tests revealed signs of distur the autonomic nervous system A deficiency hydroxyvitamin D was demonstrated, clearly to the frequency of stools and to the weight his deficiency might play a role in the ss of the polyneuropathy

polyneuropathy corneal sensitivity vibratory 25-hydroxyvitamin D obesity jejunoileal

cand 206 391 1979

last decade intestinal bypass surgery has as a treatment for massive obesity One mplications reported (1 4 5 7 8 10 12 21 22) is a polyneuropathy for which several possible causes (11)

of this study was to investigate the pres lyneuropathy by assessing the corneal a d vibratory preception in bypass tients and in controls and comparing the h various biological and psychological

UBJECTS AND METHODS

atients aged 20–57 years (mean 35) who had rgery for severe obesity between Nov 1969 76 were included in the study All had given d consent to the investigation An end to-side my preserving 50 cm of the small intestine ormed in all The jejunum/ileum ratio varied 37 5 cm of jejunum and 12 5 cm of ileum continuity The mean period since surgery 8 months at the time of the investigation

The control group comprised 21 members of the local blood donor group aged 18–47 years (mean 32)

The bypass-operated patients were on an uncontrolled diet and were routinely given multivitamin tablets con taining 1200 IU of vitamin D_2 Most of the patients re ceived other supplements such as calcium magnesium potassium folic acid and cobalamin

Patients and controls were excluded from the study if they had corneal disorders or had undergone eye surgery were using eyedrops or contact lenses had a history of either neurological or arteriosclerotic diseases or took psychopharmacological drugs or excessive amounts of alcohol

The corneal sensitivity and vibratory perception were measured without knowing whether the subjects were pa tients or controls The corneal sensitivity was tested using Cochet and Bonnet s aesthesiometer with a nylon filament with a diameter of 0 12 mm (6) By changing the length of the filament (0–60 mm) the cornea could be stimulated with different loads The centre of the cornea was chosen for application of the stimulus as described elsewhere (6 18) The results of three stimuli were recorded for each eye and the mean was used in the final analyses

The vibratory perception was registered on the pulps of the index fingers (IF) and on the great toes (GT) using a bioaesthesiometer (Bio-Medical Instrument Company Chagrin Falls Ohio) (17 18) The threshold value for the vibratory perception was read directly from a voltmeter which indicated the amplitude of the applied vibrations Three consecutive measurements of the threshold value on both extremities in lying position were recorded and the mean values were used in the final calculations

Blood samples were taken with the subjects in fasting state Serum calcium potassium inorganic phosphate and alkaline phosphatase were measured on an SMA 12/60 au toanalyser Serum folic acid and vitamin B_{12} were meas ured by microbiological assays Serum 25 hydroxyvita min D (25-OHD) was measured using a competitive pro tein binding assay (16) Normal values for 43 age matched controls for the month of the study (Oct) were 28 4±9 8

Abbreviations IF = index finger GT = great toe 25 OHD = 25 hydroxyvitamin D BDI = Beck Depression In ventory

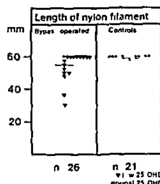


Fig 1 Absolute values of corneal sensitivity in 26 patients with jejunoileal bypass and in 21 controls Mean values are indicated by solid lines

ng/ml A single 24 hour urine sample was collected for measurement of calcium excretion

The psychological test used was part of an expanded version of the Beck Depression Inventory (BDI) consisting of a 21 item questionnaire (2) and additional 14 items constructed to detect various autonomic nervous system manifestations The items used to evaluate the autonomic nervous system were tremor palpitations constipation dryness of the mouth difficulty in urination and disturbed accommodation The items used to demonstrate psychological symptoms related to asthenia were irritability insomnia fatigability and loss of libido (1) Intensity scores 0=normal 1=mild 2=moderate 3=severe

Statistical analyses

Non parametric statistics were used Comparisons were made using the χ test and correlation coefficients by Spearman s rank correlation Mean values were used to express the overall trend of results and one standard deviation (S D) to express the scatter

RESULTS

The corneal sensitivity and vibratory perception of each patient and control are shown in Figs 1 and 2

Table I *Number of patients with jejunoileal bypass and controls with reduced corneal sensitivity (threshold <55 mm) and vibratory perception (IF threshold >5 V GT threshold >9 V)*

	Corneal sensitivity (mm)		Vibratory perception (V)			
Threshold	<55	≥55	>5 IF	≤5	>9 GT	≤9
Bypass-operated (n=26)	7	19	18	8	14	12
Controls (n=21)	1	20	3	18	3	18
χ^2 test (p<)	0 05		0 005		0 01	

Table II *Relationship of biological or psychological characteristics in 26 patients with jejunoileal bypass and the reduction of corneal sensitivity (threshold <55 mm) and vibratory perception (IF threshold >5 V GT threshold >9 V)*

	Corneal sensitivity (mm)		Vibratory perc (V)		
Threshold	<55	≥55	>5 IF	≤5	>
Stools					
≥3	6	7	1?	1	[illegible]
<3	1	12	6	7	[illegible]
p	<0 05		<0 05		<
Paraesthesia					
+	6	14	15	5	[illegible]
−	1	5	3	4	[illegible]
p	n s		<0 05		<
Muscle pains					
+	5	1	6	0	[illegible]
−	2	18	1?	8	[illegible]
p	<0 001		n s		<

Fig 1 shows that some patients had low corneal sensitivity and that overall the considerable range of results in this group shows a similar wide scatter of results in the group for measurements of vibratory pe There were significant differences between and controls with regard to corneal s (p<0 05) and to vibratory preception (IF GT p<0 01) (Table I) The patients with corneal sensitivity also had significantly di

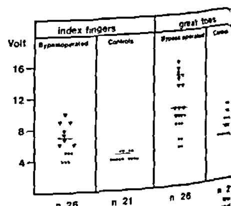
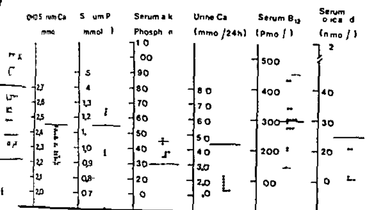


Fig 2 Absolute values of vibratory perception in 26 patients with jejunoileal bypass and in 21 Mean values are indicated by solid lines



F g 3 B ochem ca d from 26 pat ent w jejuno eal byp values + l S D by sol d and do

y percep on ($p<0.05$) No correlat ons served between advanced age reduced en v ty and v bratory percept on

logical results are shown in F g 3 The e e s we e undetectable n 2 pat ents (<2 l below the normal range n 17 The mean s was 39 1+11 0 kg in these 17 pat ents 8 3 kg n the others ($p<0.00?$) Serum o phatase was elevated in 10 patients all ad serum 25 OHD values below 10 ng/ml serum calcium concentrat on and the uri m exc e on were reduced
OHD values were s gn f cantly reduced in the pat ents w th reduced v bratory ompared w th the rest of the bypass group Reduced corneal sens tivity was l among pat ents with low 25 OHD with on whereas no correlat on was found ow 25 OHD and reduced corneal sen rum fol c ac d levels tended to be sub- w hin the lower normal l m t whereas alues were w th n the normal range no correlat on between serum fol c acid

and B 2 values and the reduced cornea or v bratory percept on

The average da ly stool frequency of th was 3 1+1 7 The number of da ly stool c sign f cantly to both reduced corneal sen t vibratory percept on ($p<0.05$) (Table II) also shows that the presence of paraesthe a related to reduced vibratory percept on (but not to decreased corneal sens tivity

Six pat ents all w th low serum 25 OHD com pla ned of pers stent muscle tenderness at rest They had s gnif cantly reduced corneal sens t vity ($p<0.001$) and reduced v bratory percept on of the lower extrem t es ($p<0.05$) compared to the rest of the pat ents

Table III shows the number of pat ents w th n each score of the psycholog cal tests related to as then a and to the autonom c nervous system The correlat on between the tems related to the au tonom c nervous system and the reduced v bratory

Dis bu on of the pat ents by intens ty e BDI

	Sco e		
	0	1 2	3
m e a ed to the nervous system	8	9	9
m e a ed	2	11	13

Table IV *Scores of tl e BDI related to the a tonom c nervous s stem and tl e relat onsl p of tl ese to corneal sens t ty (thresl old <55 mm) and v bratory percept on (IF tl resl old >5 V GT tl resl old >9 V)*

Threshold sco e	Corneal sens t v ty (mm) <55	≥55	V bratory percept on (V) ≤5 IF	>5	≤9 GI	>9
0	3	5	3	5	5	3
>3	3	6	0	9	1	
χ^2 test (p)	n s		<0 05			

perception was significant ($p<0.05$) (Table IV) No relationship was found between scores of items related to asthenia and to the reduction of sensory qualities

DISCUSSION

The present investigation revealed a reduced corneal sensitivity and vibratory perception in obese patients who had undergone intestinal bypass surgery This suggests the presence of a neuropathy affecting both the peripheral sensory nervous system (vibratory perception) and the fifth cranial nerve (corneal sensitivity) These sensory abnormalities were related to disturbances in vitamin D metabolism which again were related to frequency of stools Low 25 OHD values have previously been reported in patients operated upon with jejunoileal bypass (7 8 11 13 14 20 22) It is evident that the most severe sensory disturbances occurred in patients with low 25 OHD value but the results do not lead to any conclusion as to whether vitamin D deficiency plays a role in the pathogenesis of the neuropathy or is merely an expression of severe multifactorial metabolic disturbance Recently Halverson et al (11) however suggested that vitamin D deficiency might induce neuromyopathy in patients who have undergone intestinal bypass surgery

Muscle tenderness occurred in 6 patients all with low 25 OHD values indicating myopathy and we assume like other authors that vitamin D or its metabolites has an effect on striated muscle (3 9 13 15)

The patients with abnormal vitamin D metabolism and reduced sensory qualities also had the highest frequency of stools and the largest weight losses The desired weight reduction by jejunoileal bypass surgery was thus obtained at the expense of a severely disturbed vitamin D metabolism

Factors other than disturbances in vitamin D metabolism are probably involved in the pathogenesis of reduced corneal sensitivity and vibratory perception As shown in Table II paraesthesias were present in most of the patients and were related to reduced vibratory perception These results indicate changes in the peripheral sensorimotor nervous system which could be due to lack of vitamin B_{12} The serum B_1 levels were normal probably because the patients were receiving regular B_{12} injections since the first postoperative year (19) The folic acid levels were low ... not correlate with the reduced sensory ... Another cause of the polyneuropathy could ... of thiamine (14) although we did not mea... serum levels because none of the patients ... of the classical symptoms of thiamine def... We did not find signs of diabetes either ... might have been responsible for the po... pathy On the contrary we noticed decrease ... of fasting blood sugar compared with ... operative values which is in accordance ... observations of Solhaug and Grundt (21)

Using the expanded BDI (2) no relation ... found between asthenia or the reduced ... qualities whereas items related to the ... nervous system showed a good correlation ... reduced vibratory perception This might ... widespread changes in both the peripheral ... central nervous system

From a practical point of view reduced ... sensitivity may prevent the wearing of ... lenses Reduced corneal sensitivity and ... perception as a part of polyneuropathy is ... recognized problem which should be add... increasing number of complications recon... jejunoileal bypass surgery

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Acta Med Scand 206 39 -403 1979

Incidence of Urolithiasis Leading to Hospitalization in Finland

Markku Juuti and Olli P Heinonen

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ICT The study population consists of 2 304 sis patients discharged from all hospitals in al hospital districts in 1970 The incidence 50 per 100 000 inhabitants per year 74 for 127 for women The age distribution resem- Gaussian curve, with a peak between 45 and for men and between 50 and 54 years for The male/female ratio was 2 7 in the entire , about 1 in the age group 0–24 years about age group 25–74 years and about 1 5 in 75 years or older The standardized inci as highest in Southeastern Finland and in the ago of Åland and lowest in the coastal area western Finland In the area with high inci he age distribution of urolithiasis patients dif om that in the rest of the country In the ps over 40 the incidence of urolithiasis did ear to decrease This difference was attri some lifelong environmental exposure The dized incidence of urolithiasis leading to hos- tion was higher among urban than rural resi seasonal variation in the hospital admissions lithiasis was not evident temporal patterns of ons were however dissimilar in urban and reas, and might reflect differences in the phys- vities of urban and rural populations

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er incidence of urolithiasis has been reported inland than from some other European coun 4 7 15 17) An average of 30 per 100 000 tants per year were admitted to hospital for hiasis in 1953 and 1954 (17) The reported er of patients treated for urolithiasis in Finnish tals increased more than 100-fold in the pre 50 years or so The statistics revealed no difference in the occurrence of urolithiasis be tween patients from rural and urban areas

In an earlier study from the County of Uppsala in Sweden the incidence per 100 000 inhabitants per year was 74 5 (6) and later in Alvsborg County about 80 (1) There was no statistical difference between the rates among residents of cities and rural communities A thorough study from Czechoslovakia revealed an average hospital ad mission rate of 101 per 100 000 inhabitants per year in 1950–1954 (11) The rate was very low among agricultural workers A study from the USA showed an average hospital admission rate of 94 7 per 100 000 inhabitants per year with a range from 43 1 in Mississippi to 196 5 in South Carolina in 1952 (2)

The overall male/female ratio varies in different studies between 1 5 and 4 1 (9 12 18) Season and climate have repeatedly been reported to influence the incidence of urolithiasis (5 10 13) In a study from Leeds England (16) the rate of stone passage was about 50% higher in summer than in winter

This study based on the hospital discharge data of Finland reports the incidence of urolithiasis ac cording to age sex area of residence and season

MATERIAL AND METHODS

The study is based on the hospital discharge records regis- tered by the National Board of Health from Jan 1 to Dec 31 1970 The study population consists of all patients with urolithiasis and their controls with acute appendicitis and acute pancreatitis who were discharged from any hospital in the entire country during one year Only the first dis- charge in that year has been taken into account in the analyses Some comparisons were made between patients with urolithiasis and those with any other diagnosis

Information about the resident population grouped ac cording to age sex and central hospital district on Dec 31 1970 was obtained from the Official Statistics of Finland (14) The population at the end of 1970 was 4 622

Table I *Number of hospital admissions for uro lithiasis in 1970 in Finland*

Diagnosis	Men	Women	Total
Ureteral stone	1 643	549	2 192
Renal stone	216	187	403
Vesical stone	163	65	228
Nephrocalcinosis	54	133	187
Calculous pyelonephritis	21	31	52
Calculous pyonephrosis	5	6	11
Urolithiasis n o s	152	99	251
Total	2 254	1 170	3 324

habitants 2233658 men and 2388641 women The country is divided into 21 central hospital districts the population of which ranged from 20789 in Åland to 995854 in Helsinki

The incidence rates were standardized by the direct method When testing the seasonal variation the method of Edwards was applied (3) In view of common practice and style the term admission rate is employed here instead of discharge rate although this introduces mild inaccuracy in the case of seasonal variation

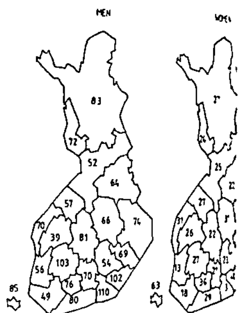


Fig 1 Standardized rates (per 100000 inhabitants) hospital admissions for ureteral and renal stones in hospital districts in 1970 in Finland

RESULTS

There were 3324 hospital admissions for urolithiasis in 1970 in Finland 2254 men and 1170 women Table I shows the distribution by different subgroups of the diagnosis In further analyses patients other than those who were admitted for ureteral or renal stone for the first time in 1970 excluded leaving 2304 patients 1650 men and women for study

The age and sex distributions of the year's hospital admissions for ureteral and renal stones in

Table II *Hospital admission rates for ureteral and renal stones by age and sex in 1970 in Finland*

	Men		Women		Total	
Age (y)	No of cases	Rate (10 ⁵)	No of cases	Rate (10 ⁵)	No of cases	Rate (10⁻⁵)
–4	0	0 0	0	0 0	0	0 0
5–9	1	0 5	1	0 5	2	0 5
10–14	2	1 0	3	1 5	5	1 3
15–19	18	8 3	22	10 6	40	9 4
20–24	79	34 2	61	27 8	140	31 1
25–29	127	74 5	54	33 2	181	54 4
30–34	149	101 9	57	39 9	206	71 3
35–39	193	138 4	68	50 1	261	94 8
40–44	229	155 8	56	37 8	285	96 6
45–49	240	183 5	68	45 7	308	110 1
50–54	155	145 2	69	52 1	224	93 6
55–59	179	162 7	63	45 7	242	97 6
60–64	135	133 5	56	42 1	191	81 6
65–69	92	126 8	38	36 0	130	73 0
70–74	37	79 7	20	25 3	57	45 5
75–79	14	55 0	18	37 1	32	43 3
80–	0	0 0	0	0 0	0	0 0
Total	1 650		654		2 304	
Mean		73 9		27 4		49 8

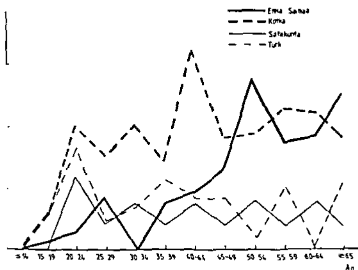


Fig 2 Hospital admission rates (per 100 000 inhabit ants) for ureteral and renal stones by age in women from central hospital districts with a high rate (Etela Saimaa and Kotka) and a low rate (Satakunta and Turku) in 1970

Table II The peak age for men was 45–49 d for women 50–54 years The male/female s 2 7 and varied somewhat with age 0–24 out 1 25–74 years about 3 75 years and out 1 5

tandardized incidence rates according to ospital district and sex are shown in Fig 1 s were highest in Southeast Finland and in pelago of Åland The rates varied similarly ct in both sexes

the sex ratio the incidence of ureteral and ones varied differently with age between stricts with a high as opposed to a low rate

For some densely populated central hospital dis tricts the age distributions of the incidence in high rate districts (Etela Saimaa and Kotka) and low rate districts (Satakunta and Turku) are shown in Fig 2 for women and in Fig 3 for men Com pared with the rest of the country there was an apparently different pattern in Southeast Finland (Etela Saimaa and Kotka) here the incidence steadily increased with age whereas in other parts of Finland the age distribution was Gaussian

The frequency of admissions for ureteral and re nal stones among residents of urban and rural com munities is given in Table III The residence area

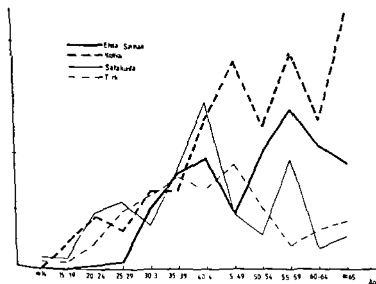


Fig 3 Hospital admission rates (per 100 000 inhabit ants) for ureteral and renal stones by age in men from central hospital districts with a high rate (Etela Saimaa and Kotka) and a low rate (Satakunta and Turku) in 1970

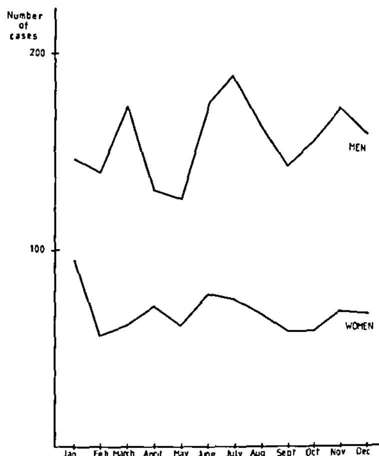


Fig 4 Number of hospital adm[...] urolithiasis by sex and month in Finland

was available in 1 898 cases (82%) The annual incidence per 100 000 inhabitants was 52 0 in the urban areas and 30 2 in the rural areas The sex ratio did not differ by the area of residence

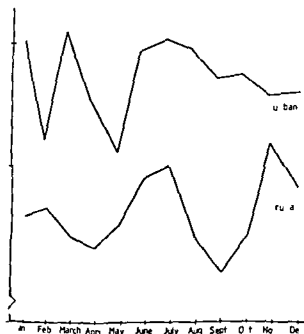
The monthly distribution of admissions for rolithiasis is shown in Table IV and Fig 4 For mparison the table also gives the corresponding admissions for acute appendicitis and acute creatitis The number of admissions for urolithiasis was largest in July and for acute pancreatitis [...] the summer months The admissions for acute appendicitis fluctuated with no meaningful trend

Table III *Standardized rates of hospital admissions for ureteral and renal stones in urban and rural communities in 1970 in Finland*

	No of cases	Population	Rate (10^{-5})
Urban			
Men	908	1 092 450	83 1
Women	308	1 247 858	24 7
Total	1 216	2 340 308	52 0
Rural			
Men	510	1 127 535	45 2
Women	172	1 130 493	15 2
Total	628	2 258 028	30 2

Table IV *Number of hospital admissions for urolithiasis acute appendicitis and acute pancreatitis by month in 1970 in Finland*

	Urolithiasis			Acute appendicitis	Acute pancreatitis
	Men	Women	Total		
Jan	149	94	243	903	[illegible]
Feb	140	57	197	818	[illegible]
March	170	61	231	831	[illegible]
April	129	70	199	83[illegible]	[illegible]
May	124	59	183	868	[illegible]
June	169	71	240	790	[illegible]
July	185	72	257	839	[illegible]
Aug	162	64	226	816	[illegible]
Sept	140	57	197	79[illegible]	[illegible]
Oct	150	56	206	839	[illegible]
Nov	166	66	232	838	[illegible]
Dec	148	65	213	793	



F g 5 Number of hosp tal adm ss ons fo urol thias s by area of res dence and month n 1970 n F nland

f adm ss ons for ureteral stones (exclud ng w th other types of urol thias s) were also ed w th adm ss ons for all other d seases n ss ons d ffered s gn f cantly for men 8 $p<0\ 001$) but not for women No stat s gn f cant variat on of adm ss ons by t me aled by Edwards method whether tested or n two- three or four month periods was the seasonal variat on among males ally sign f cant when tested in three month The results are shown n Table V The pattern of hosp tal adm ss ons for uro- d ffered between res dents of urban and eas (F g 5)

DISCUSSION

is no deal method for est mat ng the true ce of urol th as s An approach based on l adm ss ons (d scharges) clearly underest the true nc dence but s useful for relevant isons n a part cular country if the network p als s dense if the organ zat on of the hos s un form and unchanged and if the data on ions cover the ent re country adequately In d he poss b l t es for hosp tal adm ss ons are e ed to be essent ally s m l ar everywhere al beds and personnel are fairly evently d s d and med cal pract ce s carried out n a rather un form fashion To avoid any effects of pos s ble temporal changes n these factors all pat ents hosp tal zed for urol th as s in F nland during one year (1970) only were selected for the study There is no reason to bel eve that th s year was excep- t onal in any relevant way

In the past 16 years the annual inc dence of urol th as s has increased from 3 to 5 per 10000 nhab tants There is no reason to bel eve that the principles for adm ss on for urol th as s have changed strikingly during th s period However hosp tal beds and admiss ons to general hosp tals have both ncreased about twofold during th s t me (14) The proport onal increase in the inc dence is of the same order of magn tude as in a Swed sh study (1?) based on the frequenc es of roentgenolog cally verif ed ureteral and renal stones In that study the nc dence rose in 15 years from 13 to ?0 per 10000

The age d stribut on of hosp tal adm ss on rates

Table V *N mber of l osp tal ad n ss o s for re ter l st nes b seas t 1970 n F nland*

	Men	Women
Dec Feb	351	139
March–May	336	106
June Aug	403	13?
Sept Nov	369	101
χ	4 84 NS	1 8 NS

for ureteral and renal stones in this study did not differ notably from those reported earlier in Scandinavia (1) It resembles the Gaussian distribution with a peak between 45 and 49 years for men and between 50 and 54 years for women

The male/female ratio was 2 7 and varied considerably with age amounting to about 1 in the 0–24 year group to about 3 between 25 and 74 years and about 1 5 in the patients aged 75 or more

Attempts to reveal possible local differences or seasonal variations in hospital admissions for urolithiasis have not been made earlier in Finland

The standardized hospital admission rates showed marked differences between 21 central hospital districts In addition where the rates were highest (Etela Saimaa Kotka) the incidence of urolithiasis continued to increase with advancing age without any marked decline among old people This pattern was evident in both sexes This finding supports the opinion that in these areas prolonged exposure to some environmental factor(s) plays a role in the genesis of urolithiasis

The area with the highest incidence matches the area of the Wiborg rapakivi massif Also in the archipelago of Åland where the incidence of urolithiasis was relatively high rapakivi deposits are relatively common Rapakivi granites contain e g more fluoride bearing minerals than do other rocks This is clearly reflected in the ground water the fluoride content of which is about 1 3–1 9 mg/l in the coastal region of Southeast Finland and about 0 06–0 13 mg/l in other parts of the country (8)

The hospital admission rate per 100 000 inhabitants per year was 52 0 in urban areas and 30 2 in rural areas *True rates were higher since the residential* community of the patient was not available in about 18% It is however unlikely that this affected the urban/rural ratio as experience has shown that this piece of information tends to be missing at random in the data In Czechoslovakia there was a negligible number of cases of stone formers among farmers (11) This finding supports the view that the rising incidence of urolithiasis is associated with a high standard of living

Three different approaches were utilized to examine the monthly and seasonal variations in the incidence of urolithiasis Firstly the numbers of hospital admissions for acute appendicitis and acute pancreatitis served as references This comparison should reveal at least partly a possible systematic variation in hospitalization practices particularly for mild cases The monthly admissions for urolithiasis varied differently from those for the other two diseases Secondly the number of hospital admissions for ureteral calculi was compared with the admissions for all other diseases The monthly pattern for the former differed from that of other admissions in men ($p<0\ 001$) but not in women However this rather wild fluctuation in admissions for ureteral calculi did not match the seasons significantly The result does not support the hypothesis that the reason for a seasonal variation in the occurrence of ureteral calculi is s... the seasons contrast sharply in Finland ... the analyses were performed assuming ... ence a constant rate of ureteral calculi over ... According to this approach the monthly ... ences were not statistically significant

The monthly variation in the incidence of urolithiasis differed between urban and rural ... both had a peak in July but another peak ... in March in urban areas and in November ... areas This may partly reflect the physical ... of the population In men there were three p... March July and November The peak in M... due to urban dwellers only and that in N... to the rural population only This pattern ... sistent also between districts and is thus ... ered to be real This finding should howe... confirmed by other studies Also the ... that physical activity plays some role in ... rence of urolithiasis calls for a specif... study

ACKNOWLEDGEMENTS

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ANNOUNCEMENTS

The 21st Postgraduate Institute for Pathologists in Clinical Cytopathology is to be given at The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital Baltimore Maryland USA April 14–25 1980 The full two-week program is designed for pathologists who are certified (or qualified) by the American Board of Pathology or their international equivalents

The entire course is given in English and will provide an intense refresher in all aspects of the field of Clinical Cytopathology with time devoted to newer techniques special problems and recent applications Application is to be made before March 7 1980

For details write John K Frost M D 610 Pathology Building The Johns Hopkins Hospital Baltimore Maryland 21205 USA

The Second International Symposium of Nephrology devoted to Secondary Forms of Hypertension current diagnosis and management" will be held at Montecatini Terme (near Florence) Italy May 6–8 1980

Information Professor C Bianchi Centro Nefrologico Clinica Medica Generale 2 University of Pisa I 56100 Pisa Italy

International Symposium on Infections in the Immunocompromised Host will be held in Veldhoven (Eindhoven) The Netherlands June 1–5 1980

Deadlines for registration March 1 1980 abstracts mailed by March 1 1980

Further information International Symposium on Infections in the Immunocompromised Host Symposium Secretary P O Box 252 6710 BG EDE The Netherlands

Second International Symposium on Computers in Critical Care and Pulmonary Medicine will take place in Lund Sweden June 3–6 1980

Correspondence regarding abstracts papers registration and accomodation B Richardson Symposium [illegible]etary Department of Clinical Physiology University [illegible]spital S-221 85 Lund Sweden

[illegible]e II World Conference on Lung Cancer arranged by the International Association for the Study of Lung Cancer will take place in Copenhagen and Malmo June 9–13 1980

Further information Congress Secretari[illegible] Congress Service Linde Alle 48 DK 2770 Copenhagen[illegible]lose Denmark

The 5th International Conference on Synthetic F[illegible] lytic Thrombolytic Agents—Progress in F[illegible] be held in Malmo Sweden June 17–20 1980

The conference language is English and there [illegible] scientific sessions including 4 poster sessions [illegible] simultaneous sessions Conference topics will [illegible] Plasminogen activator Activation of fibrinol[illegible] and abnormal fibrinolysis Fibrinolysis and [illegible]minogen chemistry Inhibitors of fibrinolysis [illegible]lysis

Deadline for abstracts Feb 29 1980

For further particulars contact Professor [illegible] Secretary General 5th International Conference [illegible]thetic Fibrinolytic Thrombolytic Agents Co[illegible] Laboratory Malmo General Hospital S-214 [illegible] Sweden

The Seventh International Convocat[illegible]n on Imm[illegible] will be held at Niagara Falls New York USA [illegible] 1980 The theme of the program is "Immuno[illegible] Major Histocompatibility Complex"

Further information Dr James F Mohn The [illegible] Immunology Room 210 Sherman Hall State U[illegible] of New York at Buffalo Buffalo New York [illegible]

4th International Congress of Immunology of [illegible] national Union of Immunological Societies (IU[illegible] be held in Paris France July 21–22 1980

Deadline for submission of abstracts Jan 1[illegible]

Further information Congrès Services [illegible] Lefebvre F 75009 Paris France

8th International Congress of Physical Me[illegible] habilitation Disability—Prevention and [illegible] Rehabilitation Medicine will be held in Stockholm [illegible]den Aug 25–29 1980

Time limits submission of abstracts Jan 1 [illegible]finite registration May 1 1980

Correspondence Physical Medicine c/o S[illegible] Convention Bureau Jakobs Torg 3 S-111 [illegible] Sweden

Acta Med Scand 206 405–412 1979

Systemic Capillary Leak Syndrome with Monoclonal IgG and Complement Alterations

A Case Report on (1 Ep sod c S\ dro e

C G Lofdahl L Solvell A B Laurell and B R Johansson

F om he Dep ment of Med c ne Molndal Central Hosp al Molndal tl e Ins t e of Med cal M crob ology Un ers ty of L nd Lund and tl e Depar n ent of Anatomy Un e s ty of Go eborg Go eborg S eden

:T A case of the rare systemic capillary rome (SCLS) is described The patient attacks with muscle pain weakness and sweating He showed increased Hct values up and a decreasing plasma volume to about normal During the attacks the patient was in of shock and BP was unmeasurable Studies labelled albumin during attack showed an d transcapillary escape rate to about 20%/ mpared to 6% when he was without symp monoclonal IgG with a constant concentra bout 5 g/l was found Studies of the comple stem during attack showed low C4 values ations among the C1 subcomponents and C1IA complexes suggesting a complement n via the classic pathway Hereditary angio- was excluded by normal C1IA values The nent activation might be part of the patho of the increased macromolecular perme n this syndrome A short review of cases d earlier is given

rd capillary permeab l ty M components com activat on transcapillary escape rate album n d Scand 206 405 1979

drome with period c system c cap llary leak S) resulting n hypovolem c shock has been bed prev ously (1 4 9 11 12 14 15 36) The e seems to be very rare and only 8 cases been reported in the literature

t present report descr bes one more pat ent th s syndrome As noted in the pat ents de ed earl er an associat on w th a monoclonal gammopathy was found The quant tative s s of complement factors ind cated comple activat on and consumpt on during attacks

CASE REPORT

In Dec 1975 a 44 year old truck driver was adm tted to *Mölndal Central Hosp tal because of st ff pa nful muscles* and ep gastr c pa n He had for many years had symptoms of gastrit s but no pept c ulcer had been found on repeated X ray exam nat ons Otherw se he had been healthy up to March the same year From March to June 1975 he had had th ee ep sodes of t redness weakness and d aphores s Each ep sode lasted 1–2 days but d d not necess ta e hosp tal care

Major at ack In June 1975 he had had a more severe attack w th the same symptoms and was admitted to another hosp tal On adm ss on the blood pressu e was not measurable the heart rate was 150 and Hct 79% Macrodex® (500 ml dextran mean molecular weight 70000) and isoton c sal ne (2 000 ml) were g ven The symptoms subs ded w th n 24 hours Tests for adrenal nsuff c ency were negat ve No def n te d agnos s was establ shed and the pat ent was d scharged n good health

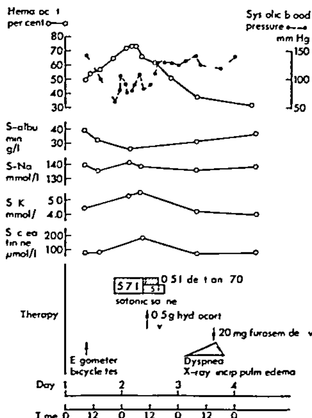
M no attacks characterized by t redness sweat ng myalg as weakness and a durat on of less than 24 hours had been frequent (3–4 per week) during the autumn of 1975 The pat ent had not ced that the attacks seemed to be el c ted by heavy work

On adm ss on n Dec 1975 Hct was 62% and BP was not measurable About 4000 ml isoton c sal ne were g ven and all symptoms d sappeared w th n 24 hours

Because of the h story of attacks be ng prec p tated by phys cal work an excerc se test on an ergometer b ycle was performed 8 days after adm ss on (F g 1) At a wo k load of 100 W the pat ent felt d zzy and h s systol c BP decreased to 60 mmHg (n t al value 140 60) He was placed n a sup ne pos t on and the BP normal zed Three hours later he became unconsc ous and had general convuls ons for 1 m n Blood sugar was normal Serum albu m n decreased from 39 g/l befo e work to 32 g/l 4 hours after work (no flu d had been adm n stered)

Neurolog cal exam nat on after the convuls ons showed no abnormal f nd ngs The BP was 100/60 H s cond on deter orated aga n later during the same day Systol c BP

Requests fo rep nts to C G Lofdahl Lungkl n ken Renströmska sjukhuset Fack S-40? 60 Goteborg 17 Sweden



F g 1 Laboratory parameters and cl n cal f nd ngs during a major attack probably elic ted by an ergometer b cycle test.

decreased to 60 mmHg and Hct increased to 65% Ringer solution (7200 ml i v) and flu d (3000 ml orally) were given during the follow ng 12 hours In sp te of this Hct increased further up to 73% There was no urine production during th s time Serum creatinine rose to 180 µmol/l d serum potassium to 5 5 mmol/l Edema of the face and extremities developed Macrodex® (500 ml) and hy sone (0 5 g) were given BP rose to 120/70 with n ? rs and the d ures s was 100 ml/hour An X ray exami nation of the abdomen d d not show any s gns of ascites

Two days after the exercise test the patient became dyspne c with basal pulmonary rales and an X ray examination showed s gns of incip ent pulmonary edema He was given ?0 mg furosemide i v and the symptoms d sappeared within a few hours

A trial of prophylactic treatment with tranexamic acid (1 g t i d) was started some days after the attack and the patient was d scharged from hosp tal There was how ever no evident effect of this treatment and m nor attacks were noted two or three times weekly

After 2 months of treatment w th tranexamic acid (March 1976) the patient was readmitted in deep shock He was cyanotic with unmeasurable BP Cardiac arrest occurred and resuscitat on w th cardiac compressions was instituted The patient soon regained consciousness Isotonic saline and Macrodex® were given and his condition normalized with n 3 days

A further treatment w h the prostagla... domethac n (25 mg t i d) was then tried for ... out any ev dent prophylactic effect Two ... occurred during th s period

The therapy was thereaf er changed to p... doses decreas ng from 40 to 10 mg dai... occurred also on th s trea ment In add... was given a β_2-adrenostimula ng drug ... creas ng doses up to 30 mg daily (Fig ... predn solone was then success ely reduced ... was om tted F ve days af er w thdrawal of ... in Nov 1976 a study of the plasma vol ... cap llary escape rate of albumin was performed labelled album n (see Methods and Resu... was then om tted and 2 days la er whe... showed s gns of a new attack the study was ... Eighty m nutes after the injection of ... I-labe... a constant infus on of terbutal ne (5 µg ... during 40 m n Oral terbutal ne was re... study was performed 4 days later when the ... without symptoms

During the following ?4 months the patient ... with predn solone and terbutaline and had ... attacks necess tat ng hospital care All ... started n connect on w th infections The las... curred ?0 months ago

METHODS

Clq Clr C3 C4 propend n and C1 esterase ... (C1IA) were determined by electroim... scribed earl er (?0 3? 33) C1IA was also d... an enzymatic test (17) C rculat ng complexes ... components were shown by crossed ... trophores s (18) Quantitative determ... performed (21) IgG IgA and IgM were ... munochem cally (8)

Album n turnover stud es were perform... labelled album n (27) The transcapillary e... albumin was determined by follow ng the ... for 1.5–2 hours The plasma volumes were ... extrapolating the activ t es to zero time The ... volumes were cal ulated from the plasma ... estimated whole body Hct (venous Hct × 0 9

Table I *Blood volume measu... during and after an attack*

	Nov 3 1976 (Before)	Nov 5 1976 (Dur...)
Plasma volume (ml/kg b wt)	39 4	?0.3
Erythrocyte volume (ml/kg b wt)	24 9	23 0
Blood volume (ml/kg b wt.)	64.3	43.3
Venous Hct (%)	43	59

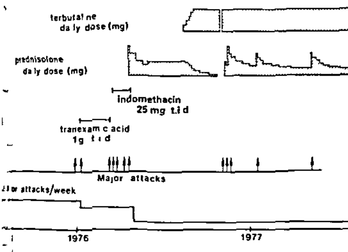


Fig 2 Prophylactic drug therapy during 2 years

RESULTS

logical findings

the attacks the patient consistently had a ct value up to a maximum of 79% in spite iderable amounts of parenteral fluid After cks the Hct values became subnormal (the observed value 27%) and normalized during wing days

eukocyte counts were increased during at The maximum value noted was 59×10⁹/l values were observed within 2 days after an The differential count during one attack 91% segmented neutrophils 0.5% banded hils 8% lymphocytes and 0.5% mono Thrombocytes were normal

marrow examined in a symptom free was normal

ndings

howed tachycardia and non specific ST and changes during attacks

findings

creatinine values were normal between at During several attacks the patient was x and serum creatinine rose to a maximum of mol/l A moderate increase in serum potas as also found A Pitressin® test between two s showed a normal concentration ability No nuria was found during the attacks

proteins

albumin was decreased at the onset of the ks As expected the lowest values (19 g/l) were observed after fluid administration On two occasions the serum albumin was measured during attacks before any therapy had been given A decrease from about 40 to about 30 g/l was recorded (Fig 1)

Albumin kinetics and plasma volumes were studied with ¹³¹I labelled albumin three times twice between attacks and once during an attack (Fig 3 Table I)

The first investigation when the patient was without symptoms showed normal conditions The plasma volume was 39 ml/kg b wt and the calculated erythrocyte volume 25 ml/kg b wt The albumin transcapillary escape rate was 6%/hour Two days later when the patient had an attack a significantly decreased initial plasma volume was found (20 ml/kg b wt) and the erythrocyte volume was 23 ml/kg b wt Hct was initally 59% and in

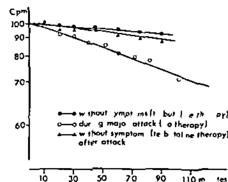


Fig 3 Disappearance of ¹³¹I labelled albumin from the intravascular compartment The transcapillary escape rate is 19%/h during attack and normal (6–8%) during other studies

Table II *Complement components other serum proteins and Hct values during different [illegible] therapy regimens*

	Reference values	March 15 1976 (Serious major attack after fluid administration)	March 17 1976 (Two days after attack)	April 1? 1976 (Moderate attack before fluid administration)	[illegible]
C1q (%)	76–136	–	87	100	[illegible]
C1r (%)	71–133	–	–	123	[illegible]
C1s (%)	72–146	–	187	138	[illegible]
C3 (%)	70–136	38	106	110	[illegible]
C4 (%)	53–207	9	74	35	[illegible]
C1IA (%)	72–153	48	150	99	[illegible]
	20–30[b]	15	–	21	[illegible]
Properdin (%)	57–153	–	–	87	[illegible]
C1r-C1s-C1IA complexes (%)	45 11–25	12		48	[illegible]
C1r-C1s complexes	Not quantitative	–	–	No	[illegible]
S-albumin (g/l)	36–54	24	41	–	[illegible]
S-IgG (g/l)	6 5–15	3 3	7 8	13 0	[illegible]
S-IgA (g/l)	0 8–2 4	0 6	1 0	1 5	[illegible]
S-IgM (g/l)	0 3–2 0	0 7	1 2	2 3	[illegible]
Hct (%)	36–48	59	33	54	[illegible]

[a] Immunochemical method [b] Enzymatic method

creased during the study to 70% This indicates a further loss of about 600 ml of the plasma volume At the end of this investigation the plasma volume was 14 ml/kg b wt (assuming a constant erythrocyte volume during this period) The albumin transcapillary escape rate was markedly increased to 19%/hour No significant change occurred when terbutaline was given 80 min after the ^{131}I albumin injection at a constant rate (5 μg/min) for 40 min

r days later when the patient was free from toms the study was repeated The plasma me was restituted (37 ml/kg b wt) A slight rease in the calculated erythrocyte volume was found from 23 to 20 ml/kg b wt The transcapillary escape rate of albumin was 8%/hour

Serum immunoglobulins (Table II) IgG was normal between attacks and during attacks when no therapy was given It was low (3 3 g/l) when plasma substitutes and isotonic saline had been administered IgA followed the same pattern IgM was increased (2 1–2 6 g/l) during attacks before fluid had been given Otherwise it was normal

Serum electrophoresis showed a monoclonal component in the anodal gamma region Immunoelectrophoretic analysis showed an IgGλ The concentration was rather constant 4–5 g/l both during attacks and in attack free periods

No abnormal proteins were found in the after concentration by polyethylene gly[illegible] or by Amicon® filtration

Complement system (Table II) Low C4 v 35 and 37% were found during two moder tacks In an attack free period C4 was n (92%) The C3 values on these occasions within the normal range During the moder tacks a disproportion was found between the centrations of the C1 subcomponents with levels of C1r and C1s compared to C1q Fu more the precipitation line appearing on the of C1s was diffusely outlined indicating a composition of the C1s precipitate compar appearance in normal serum and in serum ta when the patient was symptom free

Analysis of serum by crossed imm[illegible] phoresis showed increased amounts of C1s-C1IA complexes during attacks The of IgG were within normal limits on these sions

After fluid administration in connection serious major attack a pronounced decrease found in albumin Ig C3 C4 and C1IA T value was however more than expected from the reduct meters analyzed Four days l

	Oct 12 1977 (No symptoms on steroid and terbutaline therapy)
oms	
	74
	–
	175
	123
	73
	158
	28
	–
	40
	–
	–
	8 7
	1 2
	1 3
	–

ormalized C1 inactivator levels determined iochemically and enzymatically were within er normal range during the moderate attacks d not differ from the value in a sample ob in an attack free period Properdin was nor the samples obtained during moderate at

ellaneous During and between attacks va mandelic acid norepinephrine and epine in urine were all normal Studies of histamine ethylimidazol acetic acid during attacks did not e any increased histamine liberation

DISCUSSION

patients with SCLS characterized by a mark decreased plasma volume and hypovolemic have to our knowledge been described in the ture (1 4 9 11 12 14 15 36) In a recently shed review (1) Atkinson et al included one case described by Preston et al (29) but the se of that patient probably had another ground Five additional cases (7 22 30 34) a similar syndrome occurring in relation to cal trauma and delivery have been reported patients died in the acute attack and it is difficult evaluate whether the trauma per se might have contributed to the symptoms Therefore they are omitted in the present discussion

The 9 patients including the present one with no relation to trauma are presented in Table III Six were men and all were white The debut of the syndrome occurred in middle life There was no evidence of heredity The symptoms occurred in termittently and the duration of the attacks was 2–14 days The interval between attacks varied from 4 days to 12 months In 6 of the reported cases infection seemed to be a precipitating factor In 2 women the attack occurred premenstrually Our patient had several attacks related to strenuous physical activity

The prognosis seems to be very poor Five of 9 cases have died during an attack after intermittent symptoms for 3–8 years Two patients were alive after 3–6 years observation In 2 patients the out come is unknown

During a typical attack our patient—like cases described earlier—exhibited stiff painful muscles and some facial and neck edema indicating that the musculature and to some extent the subcutaneous tissue compartments were subjected to extravasa tion of plasma during attacks No renal leakage of protein could be demonstrated Neither were there any obvious signs indicating that the pulmonary microcirculation was affected during attacks The patient rather had episodes of incipient pulmonary edema in the recovery phase after attacks pre sumably because of hypervolemia We therefore conclude that the major cause of the increased albumin transcapillary escape rate and the con comitant plasma volume reduction was a tempo rary increase of the macromolecular permeability in the capillary beds of skeletal muscles and connec tive tissues (3 23) Accordingly we have per formed an electron microscopic study of the mi crovessels in muscle biopsies obtained both in a free interval and during an attack These findings will be reported separately (13)

The plasma volumes during attacks have varied between 42 and 74% of normal in different patients (Table III) The transcapillary escape rate of albu min during an attack was 19%/hour in our patient and 32%/hour in one of the patients described ear lier (4) Such high transcapillary escape rates seem to be unique for SCLS and are even higher than those seen in severe burns (4) Slight but constant elevations of transcapillary escape rate of albumin have been found in many other

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Ultrastructure of the Microvessels in Skeletal Muscle in a Case of Systemic Capillary Leak Syndrome

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RACT The microvessels of skeletal muscle examined electron microscopically in a case of tic capillary leak syndrome (SCLS) One biopsy taken in a free interval of the disease and one 6 hours after the onset of an attack with olemia The microvascular endothelium exhib- large number of multivesicular bodies, espe- in the specimen obtained during an attack ly this indicates a high heterophagic activity of dothelium A blebbing of the luminal surface of ular endothelium was observed in the attack men Since a complement activation seemed to during attacks the blebbing is tentatively in ted as a sign of a complement mediated injury endothelium leading to a breakdown of the lial barrier This mechanism might explain matic increase of microvascular permeability sma proteins during an attack of SCLS The gs did not indicate that the increase might de on some disturbance of the transendothelial ar transport function nor could any openings dothelial junctions, as in inflammation be strated Regionally the periendothelial basal a appeared thickened a finding which seems on in angiopathies of different kinds

ords capillary permeability complement activa electron microscopy endothelium

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previous paper (7) we described the clinical e in a case of the rare systemic capillary leak rome (SCLS) The patient exhibited severe at s of hypovolemia and shock which were elic by physical activity or infections As in other ted cases of SCLS serum analysis revealed a oclonal IgG gammopathy (see Löfdahl et al (7) references) and we also found evidence of a plement activation during attacks Extravasa of plasma probably occurred to a considerable nt in the skeletal muscles which were stiff and tender during attacks The present study accounts for electron microscopic examinations of muscle biopsies from this patient

MATERIALS AND METHODS

Small muscle biopsies were obtained surgically from the biceps brachii muscle once during a free interval of the disease (non attack specimen) and once in a hypovolemic state about 6 hours after onset of symptoms before treatment was instituted (attack specimen) Control biopsies were obtained from the deltoid muscle of a 28 year old man without any his ory of cardiovascular disease The whole biopsies were immersed over night in a mixture of 1% paraformaldehyde and 1 25% glutaraldehyde in 0 05 M Na cacodylate buffer pH 7 2 Small blocks of tissue from the superficial parts were postfixed in 1% OsO_4 in 0 1 M Na cacodylate buffer pH 7 2 dehydrated in ethanol and embedded in Epon according to routine pro cedures Sections were cut with a diamond knife on an LKB Ultrotome and examined in a Philips EM 300 elec tron microscope after staining with lead citrate and uranyl acetate

RESULTS

The ultrastructural appearance of the muscle cells and of the connective tissue compartments within the musculature of the patient appeared normal and did not differ from the control specimens Thus no degenerative changes in the muscle cells or inflam matory processes in the tissue were observed The frequency of microvessels was not quantified but there were no signs of destruction or breakdown of the endothelial tunic as has been reported in scleroderma and systemic lupus erythematosus (9)

Since the patient exhibited episodic increases of macromolecular permeability (7) the ultrastruc tural substrates for transendothelial permeation of macromolecules namely the plasmalemmal vesicles of the endothelial cells (12) and the lar junctions of the endothelium (6)

findings of Friedman and Laufer (2) who observed in the electron microscope blebbing of beating rat heart cells in culture after treatment with specific antibodies and complement In their experiments the blebbing led to a total ballooning and eventual disruption of the cells Considering the signs of a complement activation in the patient during attacks (7) the endothelial blebbing described here might represent the beginning of a complement mediated cytotoxic process leading to irreversible damage to the affected cells and thereby to an increased protein permeability The idea of an endothelial cell destruction as an important initial step in the SCLS seems to be supported by the duration of the attacks 1–4 days in our patient and 2–14 days in other cases reported (7) Such a time course could indicate that the attack does not subside until the endothelium has regenerated for example by mitoses (1) Unfortunately it was not possible to perform repeated biopsies on our patient during attacks in order to follow the development of the submicroscopic changes

In the epithelium of rat vas deferens Friend and Farquhar (3) found evidence that multivesicular bodies played the role of digestive vacuoles in the degradation of proteins that had been transported into the cells The high number of multivesicular bodies observed in the biopsy specimens from our patient may possibly represent a high heterophagic activity in the endothelium The data also indicate the possibility of a more extensive formation of multivesicular bodies during an attack than during a silent phase of the disease

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Mılıary Tuberculosıs

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[ABSTR]ACT Twenty six cases of miliary tuber[culosis] were studied in retrospect The mean age [of the] patients was 62 years Eighteen patients [suffered] from another underlying chronic disease [an]d been treated with corticosteroids or cytotox[ic drug]s. A limited manifestation of tuberculosis had [p]reviously verified or suspected in ten cases [Fever w]as present in 85% of the patients frequently [associat]ed with fatigue or abdominal pain Serum [alkalin]e phosphatase was elevated in 81% of the [patients. M]inor haematological abnormalities (anaemia [etc.) we]re found in 16 cases and pancytopenia, stimu[lated ly]mphocytes or chronic myeloid leucaemia In[... mi]liary mottling was found in the chest radio[graphs] of 13 patients Other findings were pleural ef[fusion,] mediastinal node enlargement, opacities sug[gesting] pneumonia or old, possibly tuberculous le[sions. A]ntituberculosis therapy was initiated in 12 pa[tients, t]wo of whom died within a few days There [was a hi]gh frequency of liver or system involvements [It is con]cluded that laparoscopy or liver needle biopsy [are valu]able diagnostic procedures in patients with [fever an]d elevated alkaline phosphatases of unknown [origin.] A therapeutic test with antituberculous [drugs s]hould be undertaken in suspected cases

[Key wor]ds miliary tuberculosis respiratory distress syn[drome]

[Acta Me]d Scand 206 417 1979

[In] the last three decades several authors have [drawn] attention to miliary or disseminated tuber[culosis] as posing diagnostic problems (1 9 11) [Slavin] et al (8) described 129 fatal cases in which [the pr]incipal cause of death was tuberculosis [In ab]out 30% of the cases tuberculosis was not [diagno]sed until autopsy and it appeared that [miliar]y or disseminated tuberculosis constituted the [majori]ty of these undiagnosed cases The concept [of cry]ptic miliary tuberculosis was introduced by [Proud]foot et al (11) to designate cases of dissemi[nated] tuberculosis in which the typical clinical and radiographic features were absent It seemed that a changing pattern (7 6) was becoming dis cernible in miliary tuberculosis the disease often presenting as an obscure illness in the elderly

Having recently encountered some diagnostically very difficult cases of disseminated tuberculosis we decided to study the diagnostic aspect of all relevant cases seen at Helsinki University Central Hospital and Aurora Hospital during the past 7 year period

MATERIAL AND METHODS

The material was collected with the help of the computer data on final diagnosis coded according to international practice In addition 5000 final autopsy records were examined The hospital records of all 25 cases traced in this way were available for retrospective study The 26th patient a man with miliary tuberculosis and respiratory distress syndrome was referred for treatment and in cluded in the material at a time when the present report was already under preparation

The material comprises 16 females and 10 males with a mean age of 62 years (range 41–80) The chest X rays were re analyzed by the authors

RESULTS

On admission the majority (85%) of the patients complained of fever (Table I) A body temperature of 39°C or higher was measured in 63% of the patients during the hospital stay Fatigue loss of weight and abdominal pain were each complaints of about one third of the patients Eight patients com plained of dyspnoea One of these cases calls for more detailed comments

CASE REPORT

A man aged 50 in whom cirrhosis of the liver had been diagnosed earlier presented with fever and severe dys pnoea rales being noted basally on both lung fields His arterial PO_2 was 57 mmHg on inhalation of 35% [...]

Table I *Presenting symptoms in 26 cases of miliary tuberculosis*

	No of cases
Fever (38°C)	23
Loss of weight	10
Abdominal pain	9
Fatigue	9
Dyspnoea	8
Nausea and vomiting	6
Cough	4
Headache	3

through a Venti mask The chest radiograph showed enlarged upper mediastinum faint hazy opacities basally on both sides and a small parenchymal infiltration in the right lower lobe The diaphragm was bilaterally elevated Clinically the patient suffered from the respiratory distress syndrome Neither the dyspnoea nor the hypoxia responded to treatment with digitalis, diuretics broad spectrum antibiotics or corticosteroids After a few days of antituberculosis treatment the dyspnoea disappeared and the auscultation finding was normal Within 3 weeks the arterial O_2 tension rose to 73 mmHg when the patient was breathing air The diagnosis of tuberculosis was eventually confirmed when the patient s condition allowed mediastinoscopy and a tuberculous glandular abscess was found

ESR was elevated (mean 64 8 mm/h range 14–150) in 23 out of 26 cases in 6 cases it was 100 mm/h or higher Alkaline phosphatase was elevated in 17 (81%) out of the 21 patients who underwent the test (mean 919 U/l range 318–2233) It should be pointed out that liver cirrhosis could account for the elevated value in 3 cases Serum transaminase was [illegible]mal in most cases The tuberculin test was per[illegible]d in only 10 cases 1–2 TU being positive in 3 [illegible]d 10 TU in another 3 cases

The frequency of haematological abnormalities (Table II) in this series has to be evaluated in the light of the fact that for various reasons many patients were inadequately examined The following haematological investigations had been performed tests for Hb in 26 patients total WBC in 23 differential count in 21 and thrombocyte count in 20 Bone marrow aspirate was examined in 11 patients and showed no specific abnormalities An unspecific plasma cell reaction was found in 2 patients one of whom also presented with pancytopenia In the other case of pancytopenia in our material the haematological diagnosis had been made and steroid treatment started 10 years prior to the

Table II *Haematological findings in [illegible] miliary tuberculosis*

	[illegible]
No haematological changes	
Slight changes	
Anaemia	[illegible]
Shift to the left	[illegible]
Thrombocytopenia/thrombocytosis	[illegible]
Leucocytosis	6
Severe changes*	
Lymphoid cells in bone marrow	[illegible]
Pancytopenia	[illegible]
Chronic myeloid leucaemia	[illegible]

* Only Hb was determined in two cases [illegible] WBC in one case
* Several of these findings were occasiona[illegible] one and the same patient

onset of miliary tuberculosis In 2 cases lymphoid cells were found but no specific [illegible] was made In both of these cases the diagnosis was CML in combination [illegible] nated tuberculosis

Miliary mottling was seen in the che[illegible] graphs of 11 patients (37%) (Table III [illegible] these cases the chest radiograph was [illegible] admission the mottling changes [illegible] stage In 2 cases the primary find[illegible] effusion and diffuse parenchymal infiltra[illegible] tively miliary mottling appearing onl[illegible] time In 2 cases an enlarged medias[illegible] occurred in combination with miliary

Table III *Chest radiographic findings [illegible] of miliary tuberculosis*

	No
Abnormal findings*	
Miliary mottling or	11
nodular shadowing	4
Pleural effusion	4
Enlarged mediastinal glands	
Parenchymal infiltrate interpreted	6
as pneumonia	7
(inactive pulmonary tuberculosis	1
Fibrosis (scleroderma)	
Atelectasis (carcinoma of upper	1
mediastinum)	
Normal	

* Several findings sometimes presented in [illegible] same radiograph

\ *So rce of fin l d agnosis and ground for starting treatment in 26 cases of miliary tuberculosis*

ff nal d agnos s	No of cases Total	Treatment started ex juvant bus before spec f c d agnos s was established	Treatment started after specif c diagnosis	Not treated
logical verification	2	1	1	
c anatom cal f nd ngs	4	2	2	
abo e	3	1	2	
u ure and/or X ray f nd ng alone	1	1		
	16	2		14
	26	7	5	14

n (58%) of the 26 cases were fatal (Table) o cases death was attributed to mal gnant nd the m liary tuberculosis was taken to be ary f nd ng In 14 cases (54%) tuberculosis nosed unexpectedly at the post mortem ion In 7 cases treatment had been started ibus and in 5 cases after the exact had been made (Table V) The treatment ve in almost all the treated cases In two rculosis was not suspected until miliary mottling became apparent after several weeks of severe disease Both these patients died shortly af ter antituberculosis treatment had been instituted

Three of 11 patients with symptoms for less than two months died against 7 of 15 with symptoms for a longer period

In the autopsied cases tuberculosis was found in different organs in various comb nations Typical tuberculotic changes were found in the spleen the l ver or the peritoneal glands in all cases In addi

So rce of diagnosis and course of d sease in 12 treated cases of disseminated t berculosis

M l ary mottl ng on chest X ray	D agnost c measures resulting in patholog c anatom cal d agnos s	Results of tests for M tuberculosis	Response to treatment
Present	Cutt ng needle lung biopsy (TruCut)	Acid fast smear from lung specimen pos tive sputum culture posit ve	Good d ed 3 years later from perforat on of the colon
Absent	Laparoscopy spleen b opsy	Smear and culture f om spleen specimen pos t ve	Good
Absent	Laparoscopy b opsy from per toneum and lymph node	Culture from gastric lavage flu d posit ve	Good
Absent	Needle l ver biopsy	Negat ve (sputum urine l ver spec men)	Good
Absent	Laparoscopy spleen biopsy	Negative (sputum ur ne)	Good d ed of bleed ng ven tricular ulcer 3 months later
Present	Cutt ng needle lung b opsy (TruCut)	Negat ve (sputum)	Good
Absent	Med astinoscopy b opsy from h lar lymph node	Negat ve (sputum)	Good
Present		Culture pos tive from spinal fluid and gastric lavage	Good
Present		Sputum culture negative	Good
Absent		Sputum culture pos t ve	Good
Present	Autopsy	Sputum culture pos t ve result not known unt l post mortem	D ed 4 days after in t tment
Present	Autopsy		D ed after n t t

Table VI *Chronic diseases diagnosed prior to onset of the symptoms of miliary tuberculosis in 26 cases*

	Survivors (*N*)	Non survivors (*N*)
Previously healthy	5[a]	3[c]
Chronic disease		
Emphysema and TB pleurisy previously		1[b]
Diabetes and non specific arthritis	1	
Rheumatoid arthritis		2[b]
Scleroderma and myeloid leucaemia		1[b]
Pancytopenia		1[d]
Hodgkin s disease		1[b]
Carcinoma		1[d]
Cirrhosis of the liver	2	1[d]
Chronic pyelonephritis and resection of the stomach earlier	1	
Chronic glomerulonephritis and uraemia		2
Pemphigoid erythema multiforme	1[b]	
Diabetes and recurrent cerebrovascular thrombosis		1
Schizophrenia		1
Total	10	16

[a] Includes one patient lacking IgM and IgA and with low IgG values and one who possibly had previously suffered from tuberculous coxitis
[b] Treated with corticosteroids
[c] Includes two patients with a possible history of tuberculosis disease (upper lobe calcification fistulating lymphadenitis)
[d] Treated with antitumour chemotherapy

ion involvement of the lung parenchyma hilar ds or pleura was found in all cases except one ther organs showing tuberculotic changes were the kidneys (4 cases) the suprarenal glands the heart the bone marrow (2 cases each) the brain the meninges and the lumbar spine (spondylitis) (1 case each)

In the surviving patients the important diagnostic procedures were needle biopsy of the lung (Tru Cut) mediastinoscopy laparoscopy laparotomy or needle biopsy of the liver In some of these cases therapy had been started before the diagnosis had been confirmed

Sputum specimens for bacteriologic examination had been taken from 17 cases Three of these yielded positive cultures for TB bacilli while all direct smears for acid fast bacilli in sputum were negative

Tuberculosis had been found or suspected in a total of 10 patients The diagnosis of pulmonary or glandular tuberculosis was con[illegible] in 3 patients A spontaneously healed tuber[illegible] was plausible in 7 patients in whom either [illegible] lesions in the upper lobe were found or a [illegible] of pleurisy spondylitis coxitis or fis[illegible] lymphadenitis was present One patient [illegible] history of familial tuberculosis in 11 cases [illegible] them fatal

In several cases a pre-existing disease may [illegible] contributed to the diagnostic difficulties (Ta[illegible] Three of the 16 patients who died of tuber[illegible] had previously been healthy whereas this [illegible] case in 6 out of 10 diagnosed treated and s[illegible] patients Six patients had previously been [illegible] with corticosteroids and three with cytosta[illegible]

DISCUSSION

All the patients included in this study we[illegible] sidered to be cases of miliary tuberculosis [illegible] the clinician or in the fatal instances by [illegible] thologist on the basis of the necropsy re[illegible] ficient evidence of disseminated spread of tuber[illegible] culosis was in our opinion present in all st[illegible]

Miliary tuberculosis is known to present [illegible] quently as pyrexia of unknown origin [illegible] fever is often only moderate (1 10 11) Co[illegible] patients described in other reports most of [illegible] our material ran a temperature of over 39°C [illegible] stage of the disease Loss of weight [illegible] dominal pain and dyspnoea are often [illegible] connection with miliary tuberculosis (1[illegible] supported by our findings However many [illegible] symptoms and signs in our material could be [illegible] attributed to some other co-existing disease [illegible]

Respiratory distress syndrome in connection [illegible] miliary tuberculosis has been described by [illegible] authors Most of the cases have been fatal (14 [illegible] de Silva et al (15) described a patient who [illegible] the symptoms and signs of respiratory d[illegible] appearing within 9 days of antituberculous [illegible] ment The patient with respiratory distr[illegible] miliary tuberculosis in our material is the [illegible] ond surviving case described in the l[illegible]

Elevation of *alkaline phosphatase* in se[illegible] connection with miliary tuberculosis [illegible] be a sign of infiltrative disease of the l[illegible] was found by Munt (9) in about 30% of the [illegible] reported on In our material elevated se[illegible]

...ease was found in 81% of the cases con... the results of Gneco and Chmel (3) who ...d a percentage of 86

... tuberculin test was performed in less than ...our patients All the tested cases belonged to ...oups which were not covered by the BCG ...tion scheme instituted in Finland in 1941 ...can be assumed that the positive tuberculin ...ere not a result of vaccination The results of ...e previous tuberculin tests were not avail... ...r comparison In the cases with negative ...repeated testing at a later stage might have ...positive results as indicated by Glasser et ...

...ions differ concerning the interpretation of ...ological abnormalities encountered in cases ...minated tuberculosis Anaemia leucopenia ...tosis and monocytosis have been found to ...ar as a result of antituberculosis treatment ...and can thus be directly associated with ...losis (2) Patients with leucaemic blood ...or pancytopenia in the series of Glasser et ...did not survive In many cases it may be ...to interpret whether the haematological ...ality is secondary to tuberculosis or whether ...nstituted a predisposing factor

...nia and shift to the left were the commonest ...logical features found in our material The ...aemia in one of our two patients had been ...ed several years earlier The other patient ...ed with antituberculosis drugs which re... ...recovery and disappearance of the blood ...ormalities

...ry mottling is the classical finding in the ...ray in miliary tuberculosis The absence of ...er is likely to add to the diagnostic dif... ...s In 8 out of our 14 cases diagnosed at ...sy the chest radiograph had not suggested ...tuberculosis However when re evaluated ...rospect four of these 8 chest radiographs ...veal miliary mottling Enlarged mediastinal ...have occasionally been associated with ...tuberculosis and were present in 4 of our ...This agrees with the results of Reed et al ...who found enlarged mediastinal glands in three ...adult patients

...thalmoscopy as a means of detecting chori... ...tubercles was undertaken in only one case in ...material the result being negative The bone ...ow was frequently examined but the aspirated ...ow was not fixed in paraffin as suggested by Schleicher (14) to facilitate the diagnosis of a possible tuberculosis from the marrow specimen

Most of our surviving patients were previously healthy or suffered from a chronic disease not giving symptoms indicative of disseminated tuberculosis However in many of the cases with a fatal course of miliary tuberculosis the symptoms of fever weight loss haematological changes and abdominal pain were attributable to pre existing disease In one of our cases anaemia and some months later myeloid leucaemia were diagnosed during antituberculous treatment for lung tuberculosis The antituberculosis drugs were at first thought to be the cause of the blood disorders and they were therefore withdrawn after 4 months of treatment Attention was thereafter focused on the haematologic disease and after a few weeks of steroid therapy the patient died of miliary tuberculosis This case resembles one presented by Munt (9) in which steroid treatment possibly enhanced the fatal miliary spread of tuberculosis from a previously diagnosed and treated lesion The appearance of a new severe disorder in a patient with tuberculosis may require transfer to another hospital where several diagnostic and therapeutic problems have to be solved It is understandable that the antituberculosis treatment may not be paid enough attention in such circumstances

In the fatal cases in our material the possibility of tuberculosis had—mostly because of other co existing disease—not been taken under sufficient consideration Many of the patients would eventually have succumbed to their severe chronic disease but life might have been prolonged by some months or even some years had the tuberculosis been treated Our findings give reason to emphasize the importance of starting antituberculosis treatment in time almost all the treated cases recovered The results of the applied diagnostic tests and the autopsy findings indicate that laparoscopy may be a useful procedure in patients with fever and elevated alkaline phosphatase of unknown origin In patients with diffuse pulmonary shadowing needle biopsy of the lung may be valuable If the patient s condition does not allow these procedures or if the results are negative a therapeutic test with antituberculous drugs should always be undertaken Miliary tuberculosis seems to be a condition which is chiefly found among elderly patients and which in the presence of other severe chronic diseases frequently escapes clinical detection

Table VI *Chronic diseases diagnosed prior to onset of the symptoms of miliary tuberculosis in 26 cases*

	Survivors (*N*)	Non survivors (*N*)
Previously healthy	5[a]	3
Chronic disease		
Emphysema and TB pleurisy previously		1[b]
Diabetes and non specific arthritis	1	
Rheumatoid arthritis		2[b]
Scleroderma and myeloid leucaemia		1[b]
Pancytopenia		1[d]
Hodgkin s disease		1[b]
Carcinoma		1[d]
Cirrhosis of the liver	2	1[d]
Chronic pyelonephritis and resection of the stomach earlier	1	
Chronic glomerulonephritis and uraemia		2
Pemphigoid erythema multiforme	1[b]	
Diabetes and recurrent cerebrovascular thrombosis		1
Schizophrenia		1
Total	10	16

Includes one patient lacking IgM and IgA and with low IgG values and one who possibly had previously suffered from tuberculous coxitis
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[c] Includes two patients with a possible history of tuberculosis disease (upper lobe calcification fistulating lymphadenitis)
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DISCUSSION

All the patients included in this study w[illegible] sidered to be cases of *miliary tuberculosis* ex[illegible] the clinician or in the fatal instances by [illegible] thologist on the basis of the necropsy [illegible] ficient evidence of disseminated spread [illegible] culosis was in our opinion present in all [illegible]

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Elevation of alkaline phosphatase in se[illegible] connection with miliary tuberculosis is [illegible] be a sign of infiltrative disease of the liver [illegible] was found by Munt (9) in about 30% of [illegible] reported on In our material eleva[illegible]



Fig 2 Tumour cells from infiltrate in spinal vertebra Highly pyroninophilic elements indicating the precence of RNA and active protein synthesis (methylgreen pyronin initial magnification × 240)

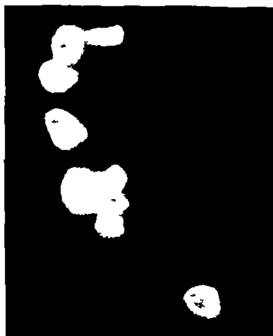
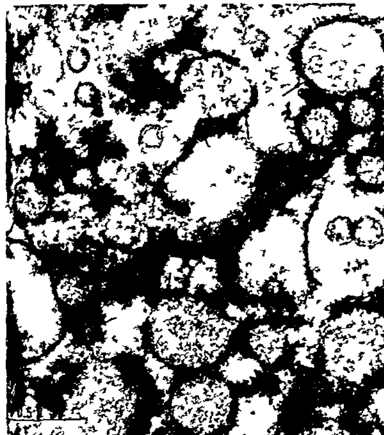


Fig 5 *Immunofluorescent* tumour cells with massive contents of IgG (kappa) Virtually all elements stained positively with FITC-conjugated anti IgG and anti kappa chains



F g 3 H gh power resolut on electron micrograph demonstrating ribosomes (arrows) attached to the out s de of the membranes sur round ng vacuoles with *amorphous material*

stly large nf ltrates of a brown sh red soft tumour w th extens ve destruction of notably the lower t and the upper lumbar vertebrae caus ng ex compress on of the spinal cord at the level of L foc of tumour t ssue were also present w th n ribs mainly on the right s de in the left il ac bone th n the base of the skull correspond ng to the right fossa.

kidneys were enlarged the right we gh ng 230 g left .85 g *They had smooth surfaces but the* areas were swollen and rather pale The other were acutely congested and no extra-osseous inf ltrates were found

nalin f xed material mounted n paraff n blocks was sed and stained rout nely with haematoxyl n and osin-saffron n add t on to h stochem cal stain ng the hylgreen-pyron n An immunoperox dase stain tect on of immunoglobul ns was also performed (P n Department of Pathology Norwegian Rad um tal Oslo)

tions of tumour t ssue from the sp ne pelv c bones nd skull showed largely dense nfiltrates of plas toid cells but also some b or multi-nucleated giant most tumour elements d d def n tely not have the rance of typ cal plasma cells (F g 1) On the other v rtually every tumour cell proved to be markedly inophil c (F g 2)

The renal glomeruli appeared normal but numerous large hyaline and ntensely pyroninophil c tubular casts were demonstrable by l ght m croscopy The affected tubules were d stended and many revealed calc f cat ons w thin necrotic ep thel al cells Multinucleated giant cells were often observed near atroph ed and/or calc f ed ep thel al elements and the surround ng interst tial t ssue showed a sl ght chron c nflammatory react on The spleen lymph nodes and l ver were devo d of any con *sp cuous changes In part cular there were no nfiltrates* of plasmacyto d cells or any ev dence of lymphoma

Electron m croscopy

Formal n fixed tumour t ssue from bone marrow (sp ne ribs skull) obtained at autopsy was postfixed n 1% os mium tetrox de in Tyrode s solut on at pH 7 4 for one hour Dehydration was carried out in graded ethanols and the samples were embedded in Epon 812 sect oned on a LKB ultramicrotome stained with lead c trate and uranyl acetate and exam ned in a Jeol 100B Electron M croscope I

The tumour cells from the base of the skull the ribs and the sp nal column all showed principally the same ultra structural features The autolytic changes were however pronounced and made the morpholog cal evaluation f cult The cells d d not reveal lymphocyt c c t cs as the cytoplasm was abundant and w th a

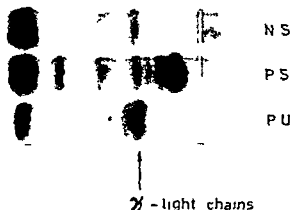


Fig 4 Agarose gel electrophoresis of the patient s serum (*P S*) and urine (*P U*) demonstrating a monoclonal paraprotein in the serum and Bence Jones protein in the urine pathological amounts of albumin were also present in the latter N S = normal serum

cytoplasmic ratio of approximately 1 3 The nuclei showed signs of autolysis with a patchy chromatin distribution A nucleolus was often present

The cytoplasm contained numerous round vacuoles often filled with an amorphous material The vacuoles were surrounded by a trilaminar membrane on the outer side of which ribosome like structures were irregularly attached (Fig 3) Typical flat cisternae of endoplasmic reticulum were almost totally absent The Golgi apparatus was either completely lacking or only remnants could be

The mitochondria were swollen with loss of matrix cristae as seen in autolytic tissues

Immunological Investigations

Studies on serum

Serum protein electrophoresis was performed in 1% agarose gel (8) Immunoelectrophoresis was carried out on glass plates in agarose gel with antibodies against IgG IgA and IgM as well as against kappa and lambda light chains Serum immunoglobulins were quantitated by the single radial immunodiffusion technique of Mancini et al (9)

Agarose gel electrophoresis (Fig 4) demonstrated a distinct M-component in the late beta$_2$-position making up 25 g/l serum The other immunoglobulins in the gamma region appeared to be suppressed as evaluated by inspection of the electropherogram Immunodiffusion verified this impression as IgA made up 2 g/l and IgM 0 4 g/l serum (lower normal range) Immunoelectrophoresis showed that the M-component belonged to the IgG(kappa) class and the results of this investigation were otherwise compatible with the immunodiffusion data.

Studies on urine

After concentration of fresh morning samples ... Filters (concentrated × 300) agarose gel electro... and immunoelectrophoresis were carried o... same techniques as for the serum samples Light... of kappa type were demonstrable by immunoe... phoresis and the light chains were located in the ... position of the electropherogram (Fig 4) ... well as Bradshaw s tests for protein were pos... significant amounts of albumin were also demo... addition to the Bence Jones protein

Immunofluorescence studies

Bone marrow specimens obtained post mortem ... transferred to EDTA-coated tubes conventional ... trifuge preparations being made with approx... 300000 cells on each slide The cells were ... with FITC-conjugated anti-immunoglobulin ... anti F(ab)$_2$ anti IgG anti IgA anti IgM ... anti IgE as well as with kappa and lambda light ... types (5) The procedure of the ensuing micros... adopted from Forre (4)

Large cellular infiltrates from the spinal col... and skull stained with anti F(ab)$_2$ and 100% of the ... tive cells stained with IgG (Fig 5) as well as with ... pa light chains No cellular elements were po... the other antisera tested Immunoperoxidase sta... ified the results of the immunofluorescence st...

DISCUSSION

The present case demonstrates several ... traits The patient had hypercalcaemia ... renal function and extensive skeletal infi... similar to those present in classical myelom... Histologically however the tumour cells ... initially classified by different pathologists ... sembling those of an amelanotic melanom... seminoma or a malignant lymphoma The... many small plasmacytoid elements and ... zarre giant cells but typical plasma cells ... found A large amount of IgG(kappa) parap... was present in serum and the urine contained ... nificant amounts of kappa type Bence Jones ... tein

The patient was only 24 years old which ... unusual in a case with the present clinical and ... munological picture The cellular pattern ... light microscopy partly compatible with ... in Waldenstrom s disease but this possi... be excluded because macroglobulinaemia ... present Waldenstrom (13) has stated that he ... has seen a patient with multiple myeloma ... age of 30 years and only a single one ... third decade Hewell and Alexanian (7) ...

d three cases of myelomatosis in patients of 1 and 22 years of age and Wille et al (14) have ly encountered a 32 year-old patient with chain disease

e gross autopsy findings were typical of classi elomatosis with extensive central skeletal ement no extra-osseous infiltrates and ristic myeloma kidneys histologically as is histochemically The other internal organs ing liver spleen and lymph nodes were all arkable The tumour elements however definitely not typical plasma cells either by or by electron microscopy Histological nation revealed massive infiltration by mainly nuclear cells of varying size and with relative ndant cytoplasm Most nuclei were more or ntrally located and there were several scat bi and multi nucleated giant cells All tumour nts were histochemically strongly pyro- bilic indicating the presence of RNA and ive protein synthesis

mortem material alone was available for the tructural studies with the ensuing limitations o autolysis The vacuoles containing the hous material most probably represent di cisternae of endoplasmic reticulum the find the attached ribosomes supporting this view hape and the size of the endoplasmic re n may also be affected by the accumulation of l distending the cisternae The almost total f Golgi structures may reflect abnormalities of tructure and function but the influence of his must be considered Altogether the ul ictural findings indicate that the tumour ele are abnormal plasmacytoid cells with ac lated immunoglobulins

immunofluorescence and peroxidase studies d that the tumour cells were producing im globulin and demonstrated that virtually all ur elements contained gamma heavy chains kappa light chains thus producing the IgG s) class of immunoglobulin found in serum rine

have thus reported a malignant immunoblas with tumour cells differing from conventional na cells but producing large amounts of immu bulin These elements cannot represent those ymphatic leukaemia because such cells seldom ain intracellular immunoglobulin and the clini icture as well as the histological pattern were incompatible with leukaemic disease Immu noglobulin containing macrophages have been re ported however but these contained lambda as well as kappa light chains

A certain amount of evidence indicates on the other hand that immunoglobulins can be formed by large pyroninophilic lymphocytes These large cells which probably made up the great bulk of the tumour masses in our patient are compatible with young plasma cells or plasmacytes

An immunoblastic sarcoma would seem to be a morphologically reasonable differential diagnosis but this condition is primarily a lymph node disease and thus not compatible with the present findings Typical Reed Sternberg cells were not observed and the findings in the current case are otherwise also not in concert with malignant lymphogra nulomatosis The reticulum cell sarcoma of bone originally described by Parker and Jackson (11) would provide a structurally satisfactory explana tion of the mononuclear cells seen in the tumour tissue of our patient To our knowledge these cells do not usually produce immunoglobulin at least not to the same extent as observed in the current case

The patient had used hashish and amphetamine regularly during the last 7–8 years previously also LSD on a few occasions The use of hashish is known to cause inflammatory disorders of notably the respiratory tract (12) but there are no available reports of a possible tumourigenic effect of this drug A case of acute leukaemia is known to have occurred in an LSD addict but a possible causal relationship remains to be established (6) Newell et al (10) found that the use of amphetamine was associated with an increased risk of Hodgkin s dis ease but no significant association was found be tween the use of amphetamine and development of this or other types of malignant lymphoma in a large series reported by the Boston Collaborative Drug Surveillance Program (3) A possible relationship between addiction to narcotic drugs and develop- ment of B-cell derived malignancies cannot how ever be definitely excluded at the present time

In conclusion the tumour in our patient appears to represent a previously unrecognized immuno- blastoma intermediate between multiple mye loma and a tumour originating from immature plasma cells The syndrome is compatible with and supports the theory that different forms of malig nant lymphoproliferative disorders correspond to different stages in the development of the B ly phocyte to the mature plasma cell

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Rheumatoid Arthritis, Immune Complex Disease, and Hypereosinophilic Syndrome

Report on a Case

G H llerdal B Marjanovic and H Åberg

F om the Department of Internal Med c ne Un ers y Hosp tal Uppsala Sweden

TRACT A patient with typical rheumatoid h s is presented After a short period of the dis- a hypereosinophilic syndrome (HES) developed asculitis pulmonary fibrosis and thrombosis he disease took a malignant course The patient thin a year after the diagnosis of HES High of rheumatoid factor were manifested and total plement (CH_{50}) was very low indicating an active ne d sease As HES has been suggested to have o mmune aetiology these find ngs are interest s positive rheumatoid serology has very rarely reported in patients with this syndrome

o ds hypereos noph l c syndrome mmune com ease rheumato d arthr t s rheumato d factor

Med Scand 206 429 1979

reosinophil c syndrome (HES) is an uncom ent ty and has accord ng to the literature variable man festat ons The aet ology is a of controversy Some authors have claimed be an autoimmune d sease (9 18 20) a hyper v ty state (14) or of neoplastic or g n (1) ever it seems clear that the syndrome can be serious and that the pat ent may run a down course w th a fatal outcome within a few years rdless of treatment (6) We report a pat ent heumato d arthritis in whom HES developed led to death w thin a year

CASE REPORT

-year-old woman had been hyposens t zed aga nst po en n the 1950s because of allerg c rh n t s w th od re ult In 1959 she had had a cutaneous erupt on ow ng adm n strat on of pen c ll n In 1968 she developed myocard t s of unknown aet ology w th subsequent complete recovery both cl n cally and electrocard o- graph cally

P esent lliness In Sept 1975 the patient presented at her local hosp tal w th fever pa n morn ng st ffness and sl ght swell ng of the wrists elbows knees and ankles She had lost we ght and complained of t redness ESR was 30 mm/h She had sl ght leucocytos s w h 8% eos noph ls but otherw se the laboratory tests showed noth ng ab normal She was treated as a case of rheumato d arthrit s f rst w th analges s and later as the symptoms deter o- rated with cort sone In the spring of 1976 the latex test for rheumato d factor (RF) became pos t ve There was a cons stent leucocytos s of about 18.0×10^9/l and an eos no ph l a of 15% The ESR had now increased to 90 mm/h

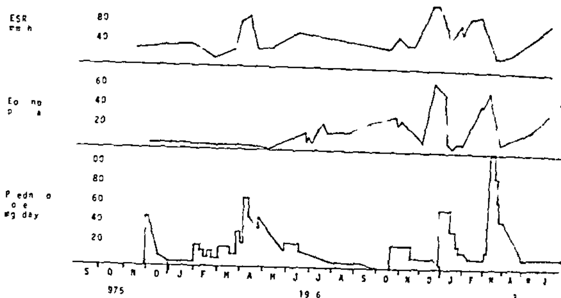
In June 1976 a morb ll form cutaneous erupt on w th tch ng occurred and the eos noph ls had increased to 18% As a drug react on was suspected all drugs except cort sone were w thdrawn In sp te of th s the pat ent had ep sodes of fever up to 39°C new cutaneous erupt ons Qu ncke s oedema and painful jo nts Th s state cont nued all the summer and general muscle weakness also gradu ally developed w th a p llow feel ng under the feet

In Dec 1976 the pat ent was referred to our hosp tal because of a thrombos s of the right lower leg verif ed by phlebography She was now cush ngo d and had an atroph c sk n w th maculopapular erupt ons n d fferent stages There were no v s ble jo nt deform t es but some jo nt movements were l m ed The heart and lungs were normal and there were no palpable lymph glands or any enlargement of the l ver or spleen

Labora ory stud es ESR was 103 mm/h Hb 105 g/l WBC 27.5×10^9/l w th an eos noph l a of 60% platelet count normal Serum ron 5 μmol/l serum transferrin 56 μmol/l serum v tam n B_{12} normal The bone marrow showed reduced iron depots and a strongly react ve pat tern w th predom nantly eos noph l c cells Electropho- res s of the serum revealed a reduced album n fract on of ?5 g l ncreased α 1 and α 2 fract ons elevated hapto glob n and normal gammaglobul ns Serum concentrat ons of IgG and IgA were normal IgM wa 2 4 g/l (normal

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Abb ev a ons HES=hypereos noph c syndrome RF heuma o d factor DECD d ssem nated eos noph lagen d sease



F g 1 ESR and eos noph l a during treatment w th pred n solone

l m ts 0 3–7 ?) IgE ?30 U/ml (normal 1 6–1??) Serum *electrolytes* were normal There was no album nuria or any leakage of prote ns into the intest ne The urinary sed ment was normal ASAT and ALAT were normal but LD was sl ghtly ra sed to 10 5 μkat/l (normal 3 8–6 7) The latex test for rheumato d factor was strongly pos t ve (1/800) Ant nuclear factor was negat ve and plasma C3 and C4 normal but total complement was s x 50% haemo-lyt c un ts (CH_{50}) (normal range 50–100) Screen ng of the blood and faeces for s gns of any trop cal d sease gave a negat ve result An ECG was unspec f cally abnormal w th w despread T wave depress ons A muscle b opsy was normal but electromyography showed unspec f c myopathy A skin b opsy revealed vascul t s w th throm s s n the small vessels and nf ltrat ons of mainly *s noph l c cell* were seen around the vessel walls rays of the hands showed bony eros ons and a reduced amount of cart lage e a p cture of *arthritis* *Chest X ray* showed inf ltrations on two occas ons and a small exudate on one occas on

Treatment and sub eq ent c se The pat ent was treated n tially w th p edn solone (60 mg/day) and anti coagulant therapy because of the thrombos s She im proved and had less pa n from the jo nts and less pro-nounced eos noph lia (70%) However a reduct on of the steroid dose to 10–15 mg day repeatedly resulted n serious deteriorat on w th h gh fever urt caria arthralg a and marked eos noph l a (F g 1 The pat ent was also treated w th a comb nation of stero ds and azath oprine (Imurel®) w thout any mprovement

In the summer of 1977 she became hoarse dyspnoe and very t red In July 1977 a course of cyclophospha-m de (Sendoxan®) was n t ated but the general cond t on gradually deteriorated and the pat ent d ed n c rculatory and resp ratory collapse

Autopsy The heart was sligh l enlarged A mural thrombos s was found n the right auricle and a embolus in a pulmonary artery The li er was enlarged w th some fatty nf l ration Old pyelonephritic scars we e found n both k dneys M croscopical were some f brous streaks in the left ven ... the lungs showed an interst t al ch onic pneum ... usual in e st tal pneumon s type and ... f bro s In the bone marrow there was e ... ph lia w th mature cells

DISCUSSION

The d se se started as typ cal rheuma ... in a woman with previous atop c ma ... Her orig nal eos noph l a of about 8 ... ible with th s atopy Eos noph lia ... degree is occasionally seen in rheuma ... (26) Ho ever more marked eosinoph ... 89%) has al o been reported in very ... rheumato d arthrit s with deformed ... frequen y of subcutaneous nod les and ... and a h gh t tre of RF (19) In our pa ... nounced eos noph l a in the blood and ... row the vascul tis and thrombosis and the ... fatal progress suggest some oth r ... t on to rheum to d arthrit s

The hypereos noph l ... synd ... various man festat ns w h eos ... blood and bone marrow and in ... organs Many excellent reviews a ... 6) Chusid et al (6) found HES to be a ...

ase with a two-year mortality of 80% regardless reatment The HES patients with the poorest gnosis are those with blast transformation in the marrow Patients with a much longer survival also been reported (10 21) as well as patients have responded favourably to steroid therapy) Other syndromes which may be regarded riants of HES are Loeffler s endocarditis (17 5 29) and Churg and Strauss allergic angiitis The pathological picture in our patient had features in common with the latter disease the most typical the granulomatosis was it

e aetiology of HES is still unknown Immune anisms may be responsible for the disease as an autoimmune phenomenon or as a reac o an exogenous antigen—or a combination h Some authors (9 18 20) have named HES minated eosinophilic collagen disease D) even though clinical or laboratory evi of what is generally regarded as a collagen e has been very sparse In the previously ed cases of DECD a positive rheumatoid ty has been very rare Our patient however very high titre of RF and an extremely low indicating an active immunological disease

ther feature of hypereosinophilic states is a cy towards multiple thrombosis In our this was manifested as thrombosis in the leg and later despite anticoagulant treatment al thrombus in the heart and a pulmonary em Ishii et al (15) wanted in fact to rename hypereosinophilic multiple thrombosis lore finding was repeatedly made in our pa namely disseminated vasculitis Vasculitis is a common complication of rheumatoid arthritis ularly in the presence of high titres of cir g immune complexes (4 12 13 16) Pulmo fibrosis which was a striking finding at au is also well known in rheumatoid arthritis ially in cases with high titres of immune com s and is in fact more common in rheumatoid is than was formerly believed (11) It is n that some immune complexes have an eosin otactic property (7 22) Thus many of the ngs in this patient—vasculitis pulmonary is arthritis and pleuritis and possibly the ophilia—can be explained by the deposition mune complexes in various organs

other interesting feature in this patient was her ity to drugs Penicillin allergy is common in many collagenoses especially systemic lupus erythematosus and Sjogren s syndrome (28) Cases in which a drug reaction has presumably triggered HES have been described (8 20) An idiosyncrasy for analgesics was also suspected in our patient Since this kind of hypersensitivity is considered to reflect a direct inhibition of prostaglandin synthesis (24 27) and thereby a rather unspecific reaction it might be speculated that such idiosyncrasy will tend to be more common when the immune system is already involved as in this case i e when the patient s reaction threshold is lower than normal

In conclusion we consider it possible that in this patient some factor—most probably an immune complex and perhaps identical with RF—stimulated the bone marrow to produce excessive amounts of eosinophils and that this production later became self regulating leading to death The disease might well have been triggered by some drug

Patients with a malignant form of HES who do not react positively to steroids might benefit from leucopheresis (8) Since immune complexes are probably involved plasmapheresis might also be tried This may be of benefit especially if performed in an early stage of the disease

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Thanks to Our Referees

Is the last number of the Acta Medica Scan ca for the decade The editors want to thank referees for all their unselfish and painstaking st in discussing the papers before they were printed On this limited space I would like to mention those colleagues among many others during the 70s who in the last two years have reviewed papers submitted for publication to our journal

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efforts of our referees have improved the of the Acta to a very high degree and it may propriate to quote the famous Swedish author Tegner with a slight travesty Where should we be if they had never been Their help has been invaluable and as we thank them we also wish them many happy new years

Jan G Wal

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INVITATION TO DISCUSSION

Diet, Lipids and Heart Attacks

et-heart theory or lipid–heart disease theory on certain correlations that have been ac as valid facts such as the relation between ity in atherosclerotic heart disease and food ption during the Second World War in cer untries and in some controlled intervention (4 10 13) Osmo Turpeinen one of the ons of the polyunsaturates for a healthy chool of thought recently reiterated this ce in the 1978 International Lecture of the an Heart Association (24) Some clinicians John McMichael and George Pickering (5 he never found the dietary hypothesis easy ept and have cited pathological or clinical nce which is brushed aside by the pro- ts of the lipid–heart theory as flimsy and not point

y then be appropriate to look a little closer vidence favoring the diet–heart theory This fore indicated as the final result of the Na ooling Project (NPP) has just been published his project was organized by most of the protagonists of the causal relation between American diet and the epidemic of coro art disease (CHD) in the USA and the West rld

of the main papers often cited as showing rease in mortality from circulatory diseases nitant with a drop in the consumption of fat form of milk butter and eggs and again used peinen (24) is the statistical study by Malm) on the relation of nutrition to health dur Second World War where he states that mortality from arterio and cardiosclerosis de in Finland Norway and Sweden during the years of the war It is clear that this is as ed with a reduced consumption of eggs butter ther foodstuffs rich in cholesterol As so other authors linking fat with atherosclerosis ros did not discuss the wartime rationing of ties and gasoline two other commodities that influence the mortality Of greater impor is however that he used the crude death rate teriosclerotic diseases leading to the rather remarkable fact that Sweden had 50% higher mor tality than the USA double that of Finland and three times that of Norway When you furthermore realize that death certificates in the 40s were signed by laymen in about 20% of deaths and that senility and uncertain causes still made up about 20% of the causes of death the figures for arteriosclerotic dis eases show up in all their uncertainty To equate the figures with CHD a disorder not yet clearly defined at that time is also impossible

Malmros is resting his whole case on the paral lelism between mortality from arteriosclerosis and fat consumption in each of these countries That (according to Malmros) the yearly per capita con sumption of total fat in the USA varied around 30 kg between 1935 and 1947 corresponding to an in creasing death rate from arteriosclerosis of 65–120/100 000 population while in Sweden the death rate varied between 125 and 160/100 000 population for a total fat consumption of 17–21 kg per capita during the same years did not lead to any comment from the author or from any of his followers

Even if the crude death rates were accurate there are still other explanations of the variability The most probable is that the decrease in arterioscle rotic deaths were due to the wartime lack of respira tory epidemics after an influenza epidemic in the late 30s This coupled with the advent of anti infectious treatment with the emerging sulfa drugs is quite enough to explain the short time decrease in mortality To use Malmros paper of 1950 as any thing more than a curious example of the lack of insight in how to use mortality statistics indicates a marked need for support of the uncertain theory

Another corner stone in the lipid–heart theory is the straight line relation between serum cholesterol and the later incidence of clinical manifestations of CHD Repeatedly it has been stressed that the low er the serum cholesterol the lower the risk (2 4 7 9 10 12 14 17 19 21 22 23 24) It has not been possible to define which level of cholesterol should be aimed at but below 200 or even 180 mg/d been mentioned (22 23) It is therefore that one of the best documented US

NPP (19) in its final report shows that the standard incidence ratio in all studies and in pool 5 was higher in the lowest quintile of serum cholesterol than in the next This led the authors to use the two lowest quintiles combined as basal risk Even the third quintile did not have a much increased risk if compared with the lowest The final result of this study using fatal and non fatal myocardial infarction and sudden coronary death as end points after 8 6 years of observation in a large sample of men 40–59 years of age, thus shows that serum cholesterol values below 240 mg/dl carry similar risks Only in the highest quintile is the risk appreciably higher In an ongoing population study in Gothenburg the risk of myocardial infarction is about the same for the four lowest quintiles of cholesterol and appreciably higher only for the highest quintile (8) This is a finding similar to what is now published by the NPP

Even though analysed in a variety of ways the lack of linearity between risk and serum cholesterol cannot be obscured Needless to say the authors—all protagonists of the diet–heart disease theory—do not emphasize this remarkable result but say it should lead to further studies One of them Stamler (22) in a review article published at the same time as the result of the NPP still uses these figures to emphasize that it is the rich American diet that causes the CHD epidemic in the USA and maintains that the ideal serum cholesterol should be way below 200 mg/dl He also maintains that there are not enough data to exactly delineate where the upper limit ideally should be This seems rather negative the NPP did not show any benefit with serum below 240 mg/dl (19)

Introduction of bias in the study

It is understandable that the authors of the many American epidemiology studies of coronary heart attacks usually do not discuss the role of the bias introduced in the studies because of the drop-out problem It is obvious that the aim of most such studies—as for example the Framingham study and the NPP—is to depict the risk situation for the whole American population at least for its middle aged men There are however a few who admit that the large amount of non responders in such studies constitute a problem in the interpretation of the results Such was the case when the Framingham study was planned in the 50s The effort to diminish the number of non responders by [illegible] families rather than individuals was [illegible] successful and might have introduced [illegible] instead Adding some volunteers after [illegible] sample had shown a response rate of below [illegible] some age categories certainly did not [illegible] the representativeness of the sample The [illegible] of this study which nowadays are published [illegible] each month in some scientific journal are [illegible] said to represent the white US population [illegible] it is not The same goes obviously for [illegible] where Framingham is the only part [illegible] population which has had enough end-points [illegible] make an analysis possible It is interesting [illegible] that Stamler (22) who is probably the most [illegible] late of the missionaries for the diet-heart [illegible] now uses the NPP in his main argument [illegible] own study of the Chicago Gas employees [illegible] demonstrated that there is very little difference [illegible] CHD incidence in relation to the original cholesterol value (final report of the NPP) [illegible]

There are however a few America[illegible] dressing themselves to the question of bias [illegible] the NHLBI study of twins and lipoprotein [illegible] base population in this study was a selected [illegible] veterans in some specific states Only [illegible] selected twins took part in the study and [illegible] ted that the responders had better [illegible] were better educated than the non responders [illegible] these features are of importance when [illegible] people according to social class in [illegible] studies

Another study of the importance of self-selection is published by Remington et al (20) [illegible] rather ingenious way of stepwise analysis of [illegible] who were willing to volunteer for a [illegible] effect of exercise training on coronary risk [illegible] concluded that they did not find any [illegible] ference between responders and non [illegible] This was at least partly due to the selection [illegible] different population groups studied [illegible] were treated somewhat differently [illegible] Nevertheless they also concluded that the sample certainly was not representative [illegible] population

It is of importance to note this bias [illegible] sive American population studies as [illegible] one of the reasons why the results do not [illegible] check with those from more careful [illegible] European studies One point of special [illegible] is the emerging of social class as [illegible]

risk factor in Europe but non-existing in ...ted American studies

...d reporting—force of persuasion?

...appreciated enough that the same persons ...e same data over and over again create the ...ion that an enormous wealth of information ...n gained over the last few decades The ...thors also emphasize that most of what is ...d supports the diet-lipid heart disease Repetition of statements that are only par...e do not become truer or more scientific by ...n alone Look at the Finnish Mental Hos...udy Two preliminary reports have been ...d the last one in 1972 (17) So far the final ...hat could be critically evaluated has not ...de public yet The final report of the NPP appeared and gives a different impression ...g for example serum cholesterol than the ...ublicized preliminary report (9) The total ...orrelation between sudden death and serum ...rol in the preliminary report has however authors to omit this analysis in the final ...here quite a lot of statistical sophistication to analyse the combined feature myocar...rction fatal and non fatal plus sudden ...y death

...ussion of the diet-heart theory and its im... for preventive measures would not be ...e without some comment on the results of ...O primary preventive trial using clofibrate This trial was carried out in Edinburgh ...st and Prague on a total of 15745 men aged ...ears at the time of entry The treatment ...onsisted of a randomly selected half of the ...ose serum cholesterol concentrations fell ...the upper third of the distribution in about ...olunteers tested The other 5000 men with ...e high cholesterol values received placebo ...ond control group comprised 5000 men ...d at random from the lower kind of the ...terol distribution The men were treated for ...rage of 5 3 years The reduction in serum ...terol concentrations in the treatment group ...ted to 9% considerably less than what was ...at (15%) In the groups within the high range ...lesterol concentration clofibrate made no dif...e to the incidence of fatal heart attacks nor ...ere a significant difference in the incidence of ... There was however a definite reduction in ...cidence of non fatal myocardial infarcts in those who received clofibrate This reduction was greater in men with the higher serum cholesterol values who also showed the greatest reduction in their serum cholesterol concentrations While this study showed a reduction in non fatal infarcts the overall impact of clofibrate on death rate apparently was adverse Both number of deaths and the crude mortality rates from all causes in the clofibrate treated groups were significantly higher than in the control group

An editorial in the British Medical Journal (3) concludes The immediate practical conclusion must be that clofibrate can no longer be recom mended as a lipid lowering agent for general use (though it may still have a place in treating specific hyperlipidemias) Furthermore since there are so many unanswered questions the other lipid lower ing regimens recommended for general use may possibly share the same problems and regimens of this kind—including perhaps dietary modification with polyunsaturated fats—will require equally careful consideration in the future if we are to achieve benefit without at the same time causing more harm than had individuals been left un treated

The main arguments for preventive measures against CHD now before we have solid evidence that these measures will prevent this type of heart disorder have been 1) that they do not increase risks and do not entail any risk and 2) that they are aimed at preventing sudden death the presentation of CHD that cannot be treated as the victim suc cumbs within the first hour (2 21)

If we look more in detail at the arguments for change in diet now before any evidence is there it may be that change in diet is without risk for the individual although even this has been questioned (3) It may be another question for the community especially those societies where agricultural production is of importance both for the economy and for the social welfare of a large part of the popula tion Without getting too deep into the results of widespread dietary changes for the agricultural in dustries it is enough to point out that it is reason able to have well founded arguments when interfer ing with a large part of the society regarding work employment and income

When it comes to prevention of sudden death it is quite clear from many studies that about 60–70% of deaths from CHD occur outside hospital and are unattended This means that this group al

prises about one half to one third of all instances of CHD. *At a closer look, about two thirds of these* deaths have already had some earlier manifestation of the heart disorder, mostly a recognized myocardial infarction. Many studies have demonstrated that the prognosis towards prolonged life in those cases depends on the size of the infarct and the continuation of smoking. Diet or blood lipids are of no consequence for the final outcome in these patients.

Furthermore, if you look at the correlation between the common risk factor and sudden death as the first sign of CHD, for example in the American Pooling Project, there is no straight correlation between serum cholesterol values and sudden death (9). On the contrary, all values below 250 mg/100 ml have the same risk for sudden death and all above 250 the same somewhat higher risk. In contrast to the other risk factors—elevated blood pressure and smoking—serum cholesterol values bear no straight line correlation to the occurrence of sudden death within 10 years (9). The authors who are most interested in promoting diet changes are obscuring what they themselves demonstrate by correlating to all three risk factors, or by correlating serum cholesterol to all new events of CHD. The argument that dietary changes should postpone sudden death has no background even in the best and often quoted American study (9).

It has been shown that at least some β adrenergic blockers diminish the incidence of sudden death after myocardial infarction (25). The clear-cut results with these medicines should be compared to the ambiguous results with diet or lipid lowering [illegible]. The repeated demonstration that manipula[illegible] of the serum cholesterol value in man does not [in]fluence the mortality rate differs considerably from the demonstration that β blocking agents, or at least alprenolol and practolol, do decrease the incidence of sudden death in patients after myocardial infarction and coronary deaths in patients with moderate hypertension. Is there any way of reconciling these different results?

The use of mortality from heart attacks as an end point for an agent possibly acting on atherosclerosis can be criticized. The complex nature of most heart attacks, involving pathophysiologic mechanisms both in vessels and myocardium, makes it impossible to equate degree of vascular changes with end organ failure. The myocardium, especially *under ischemic conditions*, may be very sensitive to catecholamines and adre[illegible] *fluences rather than ischemia may lead* [illegible] ultimate fatal outcome. All evidence [illegible] interpreted that high cholesterol concen[illegible] (highest quintile or upper third) may le[illegible] myocardial infarction, which can be pr[illegible] through a modest reduction of serum ch[illegible]

Death—especially sudden unexpected [illegible] other hand, bears no relation to serum [illegible]terol values but is due to sudden [illegible] catecholamine influence on the heart. [illegible] can be protected to some extent a[illegible] β adrenergic blocking drugs (25). Su[illegible] tation takes into consideration the d[illegible] tween vascular changes and the myocar[illegible] in conformance with the final results of the [illegible] the clofibrate trial and points to a reason[illegible] continuation of studies on the mode of de[illegible] heart attacks (1, 2, 3). It does not give any [illegible] to the idea that changes in diet would de[illegible] incidence of sudden death or fatal myocar[illegible] farction and confirms thus also the results [illegible] trials.

Science is progressing through original re[illegible] consisting of formulating and testing hypot[illegible] adequate surroundings. The recent st[illegible] ing the etiology and pathogenesis of hear[illegible] ischemic heart disease, and arterioscler[illegible] started in a similar way with formulating [illegible] eses looking for confirmation in labora[illegible] Some testing of these hypotheses has a[illegible] done in widespread population studies. [illegible] nately many, if not all, of these studies [illegible] ratories and populations have lacked a[illegible] *definition both of the end points of dise[illegible]* the role of the many factors studied. The [illegible] such studies have been inconclusive, [illegible] leaders dissatisfied and frustrated ([illegible] 17, 21, 22, 24). *They have become* m[illegible] interested in advocating interference [illegible] people live as "we cannot wait until we ha[illegible] tific proof" (2). The hypotheses to be te[illegible] thus taken over as the most probable [illegible] advocated now is that we should be [illegible] only on the belief of the scien[illegible] field (21, 22, 23). Committee reports f[illegible] countries or answers to ques[illegible] come the most important part of the [illegible] to persuade politicians about the [illegible] approach.

Scientific results can never be [illegible]

!a comm ttee or answers to questionnaires e to resort to comprom ses arrived at in tee meet ngs by themselves shows the ss n the argument for the proposed actions

Lars Werko Sodertalje Sweden

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Effect of 24-Hour Somatostatin Infusion
1Glucose Homeostasis and on the Levels of Somatom...
and Pancreatic and Thyroid Hormones in Man

P F Lins S Efendic and K Hall

From the Department of Endocrin l y Karo nska H sp al S kh lm s

CT In order to investigate whether
atin plays a role in the regulation of thyroid
secretion we have compared the effects of a
d somatostatin infusion on insulin and
levels on the one hand with its effect on
T and TSH on the other Furthermore the
vels of somatomedin A were determined
as infused in control experiments Cyclic
atin was given as an i v bolus of 200 μg
by a constant rate infusion of 50 $\mu g/h$ during
Somatostatin suppressed basal insulin and
levels as well as insulin responses to meals
ot influence somatomedin A levels T_4 and
sed during the first hour whether somato-
s given or not. Thereafter T_4 and T_3 re-
table in the control experiments while they
to decrease slowly when somatostatin was
he suppressive effect of somatostatin was
) 33 hours ($p<0.05$) and 24 hours ($p<$
er the onset of the infusion In contrast
TSH were not suppressed by somatostatin
hat basal TSH did not decrease favors the
the suppression of T_4 and T_3 was mainly due
t inhibitory effect of somatostatin on the
land Our observation that a low dose of
in decreases peripheral T_4 and T_3 levels
the idea that somatostatin plays a role in the
of thyroid hormone secretion

somatostatin thyroid hormones insulin
omatomedin

cand 206 431 1979

etapeptide somatostatin is widely dis
the body in endocrine like cells and in
sues (13) Thus somatostatin-containing
und in the islets of the pancreas in the
f the gastro ntestinal tract and in the
ed. There are two types of evidence sup-
idea that the peptide plays a physiolog
ical role in the islets and in the
enously administered som t stat
presses the release f insu n glu
intestinal hormones ( ) Secondly
somatostatin from the p it creas an
testinal tract could be mod fied b
and hormones as well as by the au
system (8 9 15) On the other han
whether somatostat n plays a role n
of thyroid hormone secret on

We have therefore compared the ef e s
longed somatostatin infus on on in ul
glucagon levels on the one hand with tho e n
thyroxine (T_4) triiodothyronine (T_3) reverse
triiodothyronine (rT_3) and thyrotrophin (TSH) on
the other In addition an insight into the effect of
the peptide on growth hormone (GH) secretion was
gained by following the serum levels of somato-
medin A (SMA)

STUDY POPULATION AND METHODS

Eleven healthy volunteers three women and eight men
aged 28–47 years participated in this study All had a
normal body weight within the range of 76–101% of ideal
body weight (Geigy Scientific Tables) The experiments
started at 7 a m after an overnight fast with the subjects in
recumbent position Teflon catheters were inserted into a
superficial brachial vein of each arm and kept patent with
a slow drip of saline During the first six hours the subjects
were fasting lunch was served at 1 p m dinner at 6 p m
and an evening meal at 10 p m In the somatostatin ex
periments the peptide was given as a priming dose of 200
μg i v at 7 a m followed by an infusion of 50 μg/hour
during 24 or 25 hours In the control experiments saline
was given alone

Abbreviations T =thyroxine T_3=triiodothyronine rT_3=
reverse T_3 TSH=thyrotrophin GH=growth hormone
SMA=somatomedin A

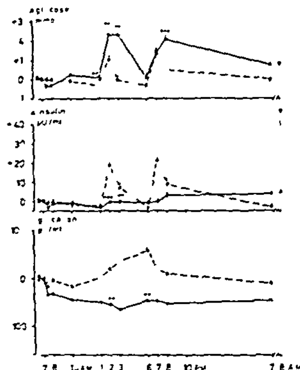


Fig 1 Effect of somatostatin (200 µg i v + 50 µg/h) on glucose insulin and glucagon in healthy subjects (M±S E M n=11) Somatostatin was given during 24 hours In five subjects the infusion was prolonged for one hour ● — = Experiments with somatostatin O - =control experiments *p<0 05 * p<0 01 *p<0 005

Blood samples were collected at 6 30 7 8 10 a m at 1 2 3 6 7 8 p m and at 7 a m In five subjects the infusions were prolonged for one hour and additional blood samples were taken from them one hour after the breakfast at 8 a.m on the next day In these subjects hematocrit values were determined throughout the experiments

Blood glucose was analysed by a glucose oxidase (14) and insulin was measured by a double antibody radioimmunoassay technique (11) Plasma g was analysed by a charcoal separation radioimmu technique (10) SMA was determined by radiorr say (12) T_4 T_3 TSH and rT_3 in serum were det by radioimmunoassays using commercially avail (Pharmacia, Uppsala Sweden)

Cyclic somatostatin was provided by the Rese partment of the Kabi Group Stockholm

Student s t test was used in the statistical analy

RESULTS

Effects on blood glucose insulin glucagon and somatomedin A

During the first hour somatostatin infusion a slight hypoglycemia which after transi moglycemia turned into hyperglycemia (Simultaneously basal insulin and gluca creased The luncheon and dinner were foll hyperglycemia which was significantly m nounced in the somatostatin than in th experiments (Fig 1) The hyperglycemia w pronounced two hours postprandially

The insulin responses to the meals w pressed by somatostatin The diabetogenic somatostatin was also evident at the end experiments Thus fasting glucose levels w nificantly increased and the glucose resp the breakfast exaggerated

SMA remained stable in the control exp Somatostatin did not influence SMA throu experiments (Fig 2)

Effects on T_4 T_3 rT_3 and TSH

The levels of T_4 and T_3 decreased during hour in the presence and absence of som (Fig 3) Thereafter they remained stable in

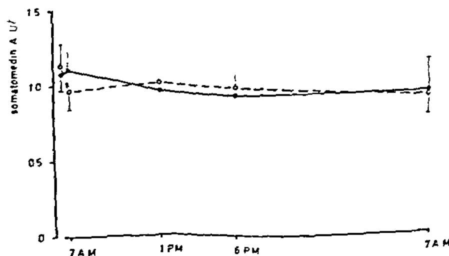


Fig 2 Effect of s tin (200 µg i v +5 serum levels of SM S E M n=11) S as in Fig 1

fect of somatostatin (200 μg i v +50 $\mu g/h$) on levels of T_4 T_3 rT_3 and TSH ($M \pm$S E M $n=11$) ■=Meals Other symbols as in Fig 1 *$p<0.05$ * $p<0.01$ ** $p<0.005$

:riments while their serum levels de lowly when somatostatin was added The ive effect of somatostatin was significant ($p<0.05$) and 24 hours ($p<0.005$) after of the infusion

nonstrated in Fig 4 the effect of somato- T_4 and T_3 levels could not be accounted for by changes in the hematocrit values In contrast rT_3 levels were slightly higher in the somatostatin than in the control experiments (Fig 3)

As expected TSH was low in the euthyroid subjects (Fig 3) During somatostatin TSH seemed to be somewhat lower than during the control experiments but the difference was never significant

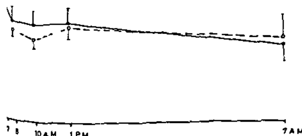


Fig 4 Effect of somatostatin (200 μg i v + 50 $\mu g/h$) on hematocrit values ($M \pm$ S E M $n=5$) Symbols as in Fig 1

DISCUSSION

In the fasting state in humans prolonged administration of somatostatin inhibits basal insulin and glucagon throughout the infusion period (17) It also exerts a slight short lasting hypoglycemic effect which turns into significant hyperglycemia approximately 3 hours after initiation of the somatostatin infusion (17) *The present study confirmed* these observations and demonstrated that the deterioration in carbohydrate homeostasis induced by somatostatin was even more pronounced in the *postprandial situation Maximal hyperglycemia* was attained two hours after the meals

The hyperglycemic effect of somatostatin was probably at least partially masked by the simultaneous *hypoglucagonemia It was recently de*monstrated that restoration of basal glucagon levels during somatostatin infusion by administration of as low a dose of glucagon as 0 5 ng/kg/min significant*ly enhanced the hyperglycemic effect* of somatostatin (16) The same dose of somatostatin as delivered in the present study also suppressed glucagon levels over a 24-hour period in diabetics (5)

In contrast to its prominent effects on insulin and glucagon release somatostatin did not suppress SMA levels Since surgical hypophysectomy leads to prompt and significant reduction of somatomedin and since the half life of SMA in serum is about 12 hours (3) this finding implies that somatostatin administration had no major effect on the release of GH in our subjects This is in accordance with observations by Christensen et al (5) who were nable to achieve a permanent suppression of GH diabetics treated with the same dose of somatostatin for 24 hours

The finding that prolonged i v administration of somatostatin decreases T_4 and T_3 indicates that the peptide may play a role in the regulation of thyroid hormone secretion However the site at which its inhibitory action is exerted is not revealed The lack of effect of somatostatin on basal TSH in this study as well as in many other reports (4 6 20) favors the idea of a direct inhibitory effect of somatostatin on the thyroid gland Weeke et al (21) who suppressed the *nocturnal peak of TSH levels by* somatostatin administered the peptide in a dose six times higher than in our study The idea that a direct inhibitory effect of somatostatin on the *thyroid gland is of prevailing importance for the* suppression of T_4 and T_3 is further supported by previous findings that somatostatin inhibits both and T_3 responses to exogenous TSH in vitro and in vivo (1 18)

Since rT_3 and T_3 are mainly formed by con sion of T_4 the difference between the effect somatostatin on rT_3 and T_3 might indicate somatostatin also interferes with the deiodina process In this context it is of importance to that Ahren et al (1) could not demonstrate effects of somatostatin on the elimination of labelled T_4 and T_3 in mice

Regardless of how the suppressive effec somatostatin on *T_4 and T_3 is mediated* it is ob from the present study that it is characterize early onset and that it seems to be permanent

In conclusion our observation that a low de *exogenous somatostatin influences the lev* thyroid hormones supports the idea that somat tin may play a role in the regulation of th hormone secretion

ACKNOWLEDGEMENTS

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Diagnostic Sign of Hyperglycemia Persistent Movement of Neutrophil Granules

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RACT This study describes a functional in the blood of diabetics the motility of neu granules in vitro When heparinized blood patients with diabetes mellitus was kept in capil ubes for 24 hours a rapid and intense move of the granules in the neutrophil leucocytes was rly seen In blood from normoglycemic dia and normal subjects, no granular motion was 24 hours but in these cases prolonged motion be induced by the prior addition of glucose

rds diabetes mellitus neutrophil granule move hyperglycemia

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anules of neutrophils are known to oscillate for a short time when viewed free floating cover slip This Brownian movement is less μm and is often increased in hypotonic solu rapid movement of greater amplitude in a group of granules has also been described e have studied the movement of granules in utrophil leucocytes kept in a sealed rectangu pillary tube The oscillation of granules in from healthy subjects and patients with var iseases decreases with time and has usually eared within 3–8 hours In patients with dia mellitus however the movements of granules ue for 24 hours

MATERIAL AND METHODS

emicals studied were added (0 01 ml) to one ml of nized blood of fasting individuals Buffy coats were prepared and drawn into fine capillary tubes (Micro-005 Vitro Dynamics Rockaway N J) sealed and 37°C until viewed under a Leitz phase interference scope (3)

Compounds added glucose 0 25 0 5 1 and 3 mg in 0 01 ml saline per ml blood neutral red and toluidine blue 0 1 mg in 0 01 ml saline per ml blood

PATIENTS

Thirty patients (ages 40–76) with diabetes mellitus 8 were treated with insulin 12 with oral antidiabetics and 10 simply with dietary control of carbohydrate intake

Forty non-diabetic subjects (ages 25–78) served as controls They were either healthy hospital personnel or patients with various skin disorders or infections

RESULTS

A fine Brownian movement of the neutrophil granules was seen in all the subjects during the first few hours It was most evident in the cytoplasmic projections both the protopods and the uropods which were seen in the moving cells After 24 hours the movement of granules as seen with 500× magnification had ceased in all controls except in an occasional neutrophil that had phagocytized a red cell When neutrophils were viewed under higher magnification (1 250×), a very slow motion could be detected in the protopods or near the surface of a few neutrophils

In patients with diabetes and an elevated blood sugar (7 0–20 1 mmol/l) a rapid movement of fine granules was seen after 24 hours (Fig 1) The granules were moving rapidly around in the whole cell or in certain areas moving around with a greater amplitude than before The larger granules moved slightly and slowly reflecting collisions with the smaller ones as did the vacuoles The movement was even more evident than at 4–8 hours and was easily seen in most neutrophils even at a magnifi tion of 500× The movement occurred not o the cytoplasmic projections but in the w



Fig 1 Three neutrophils with moving granules blood from a patient with diabetes and hyperglycemia. The thistle-like body is fibrin formation around a monocyte. Such a type of fibrin formation is mainly seen in diabetics

regardless of whether they were round or elongated. Many of the neutrophils with intensively moving granules were swollen which also made the movement easier to detect. The movement could still be seen at 48 hours in some cases

In the blood of these diabetics some darkly stained granules could be seen moving during the first hours when neutral red had been added to the ... The stain was later seen in the large non ... granules and vacuoles. The movements of ... granules in neutrophils having phagocytized ... ral red continued unabated. In dead neu... as evidenced by the uptake of toluidine blue granular movements had ceased. None of the granules of the eosinophil or basophil leucocytes from diabetics were motile at 24 hours

In four patients with insulin treated diabetes and normal blood sugar no movement of the neutrophil granules was seen at 24 hours. Upon the addition of 3 mg of glucose per ml blood the neutrophil granules showed an intensive movement identical to that seen in hyperglycemic patients. When 1–3 mg of glucose was added per ml blood from controls granular movement was also present after 24 hours in neutrophils from 28 of 30 non-diabetics. No effect on granular movement was seen after the addition of only 0 25 mg glucose but when 0.5 ... glucose was added a granular movement wa... in neutrophils from 4 of 10 subjects. No eff... the granular movement was seen following the ... tion of killed bacteria lipopolysaccharides in saline or water to blood samples

DISCUSSION

The main cause of the prolonged moveme... granules in the neutrophils observed in pa... with diabetes mellitus appears to be hypergly... as the phenomenon could be reproduced in n... cells by addition of glucose to the blood b... isolation and incubation of the leucocytes. Th... cose gives the cells energy to live longer ... they probably die more slowly and differently ... those with normal glucose levels. The cell ... brane changes its permeability and both cell ... granules seem to take up more water and s... This makes it easier for the granules and vac... to move and be seen. Changing the environme... the neutrophils by the addition of 10% salt ... saline was not found to influence the moveme... granules. Degranulation of neutrophils has bee... scribed after exposure to bacterial products ...

n did not, however influence the movement of es in our study

believe that the granular movement described s unique for diabetes with hyperglycemia as it t been seen while screening over 500 patients rarious other diseases This morphological the blood of such diabetic patients might be a tool for further studies of diabetes

ACKNOWLEDGEMENTS

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The Effect of Sulfasalazine and Its Active Components on Human Polymorphonuclear Leukocyte Function in Relation to Ulcerative Colitis

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ABSTRACT Sulfasalazine and its active components 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP) are potent modulators of inflammatory reactions but with somewhat different modes of action. Investigating the effect of these compounds on human polymorphonuclear leukocytes in vitro we show inhibition of different stages in the phagocytic process, such as migration (sulfasalazine and SP) superoxide production (sulfasalazine and SP) myeloperoxidase mediated iodination and cytotoxicity (5-ASA and SP) It is thus suggested that sulfasalazine is not just a vehicle for delivering its active components in the colon but that its therapeutic effect in ulcerative colitis and other inflammatory diseases is a result of the concurrent action of the three compounds

Key words polymorphonuclear leukocyte sulfasalazine aminosalicylic acid sulfapyridine myeloperoxidase ulcerative colitis

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Sulfasalazine formerly known as salicylazosulfapyridine (Salazopyrin® Azulfidine®) consists of 5-aminosalicylic acid (5 ASA) and sulfapyridine linked together by an azo bound The combination of a sulfonamide with a salicylate radicle was introduced by Svartz for the treatment of rheumatoid arthritis and ulcerative colitis (29) The therapeutic effect in ulcerative colitis has been verified by several clinical investigations (4 11 12) In rheumatoid arthritis however the preparation is not effective enough

Although sulfasalazine has been used successful in clinical practice for more than 30 years its mode of action is still mainly unknown It is often regarded as a vehicle for delivering its possible active components to the colon in higher concentration than could be achieved by oral administration of either one alone (10 24) About 70% of the sulfasalazine reaches the colon intact where it undergoes reductive cleavage at the azo linkage releasing 5 ASA and SP (27) The split is induced mainly by the colonic bacteria (1) All SP is virtually absorbed from the colon metabolized and then excreted in the urine Some part of 5 ASA is also absorbed but the main unabsorbed part is excreted in the faeces (24 27)

Recent investigations have regarded 5 ASA as the active moiety during sulfasalazine treatment Azad Khan et al (2) showed that local administration of 5 ASA resulted in a significant improvement in patients with ulcerative colitis whereas SP had little effect Nevertheless the beneficial action of sulfasalazine is far from elucidated

The present investigation of the effect of sulfasalazine on the function of polymorphonuclear leukocytes (PMNL) was initiated from our earlier observation that dapsone a sulfone analogue to SP has a specific effect on the function of PMNL (28) and has been used as a substitute for sulfasalazine e g in Mb Crohn (30) Since ulcerative colitis is characterized by an acute mucosal inflammation dominated by PMNL accumulation the effect of sulfasalazine on PMNL activity was relevant to analyse Our results reveal that sulfasalazine as well as 5 ASA and SP inhibits different stages in the phagocytic process such as random migration

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Abbreviations 5 ASA=aminosalicylic acid SP=sulfapyridine PMNL=polymorphonuclear leukocytes KRG Krebs Ringer phosphate buffer containing glucose FITC–fluorescein isothiocyanate PBS=phosphate buffered saline TCA–trichloroacetic acid STZ=serum treated zymosan SOD=superoxide dismutase MPO=myeloperoxidase

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phagocytosis myeloperoxidase (MPO)-mediated iodination oxidative metabolism and cytotoxicity We thus show that both sulfasalazine and its components are potent modulators of inflammatory reactions but with somewhat different modes of action thereby complementing each other s qualities These findings are discussed in relation to the therapeutic effect of sulfasalazine in ulcerative colitis as well as in other inflammatory processes

MATERIAL AND METHODS

Leukocyte preparation Blood was obtained from apparently healthy adult volunteers (age 18–35) and the leukocytes were isolated according to Boyum (5) using Hypaque-dextran sedimentation for the separation of cells from EDTA blood After separation washing and hypotonic lysis of contaminating erythrocytes the leukocytes were suspended to 1×10^7 cells/ml in Krebs Ringer phosphate buffer containing 5 mM glucose (KRG) pH 7 2 A differential count was performed to determine the number of PMNL Trypane blue exclusion was used to assay viability

Motility measurement system Leukocyte motility was studied by a modification of the method described by Nelson et al (22) Briefly agarose was dissolved (1.5%) in sterile water by heating After cooling to 50°C the agarose was mixed with an equal volume of prewarmed Gey s solution in twice its usual concentration Of the agarose medium 8 ml were poured into 60×15 mm tissue culture dishes (Flow Laboratories Irvine Scotland) Six sets of three wells were cut in the agarose The wells had a diameter of 2 4 mm and in each set they were placed 2 4 mm apart The drug tested was mixed with the Gey s solution to obtain the same concentration of the drug throughout the agarose

In each set of wells were placed 10 μl of the cell suspension (5×10^7 PMNL/ml) in the middle well 10 μl of Gey s on in the inner well and as an attractant 10 μl of normal serum in the outer well When normal is incubated in the agar chemotactic factors are ted (26) To determine random locomotion of the L population both the inner and the outer well was led with Gey s solution The dishes were incubated for 2 hours at 37 C After fixation in methanol for 30 min the agarose was removed and the cells stained with Giemsa for 15 min The distances of migration were measured with an ocular micrometer

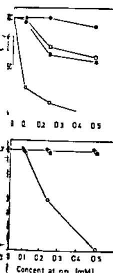
Phagocytic uptake The ability of isolated PMNL to ingest heat killed fluorescein isothiocyanate (FITC)-labelled yeast cells (Saccharomyces cerevisiae) was assayed as described by Hed (15) Briefly isolated PMNL were allowed to adhere to glass slides and non adhering cells were removed by washing To the monolayers were added 0 1 ml of FITC-labelled yeast cells (2.5×10^8 cells/ml) in KRG The yeast particles were preopsonized with 10 μg/ml of anti yeast IgG The reaction mixtures were then incubated at 37°C in a humidified chamber After 30 min the slides were washed and kept in cold (4 C) phosphate buffered saline (PBS) until examined under the microscope To separate ingested yeast cells from those tached a drop of crystal violet (0 5 mg/ml in 0 15 NaCl) was added The dye stains and thereby extinguis the fluorescerce of the attached particles but does reach the intracellular ones which still fluoresce combining fluorescence and phase-contrast microsc the number of attached and ingested particles is de mined One hundred cells were counted and the ph ic uptake was expressed as the number of yeas ingested per PMNL

Measurement of leukocyte iodination was essentially as described by Olsson et al (23) The rea mixture contained 1×10^6 leukocytes 10% pooled hu serum 30 nmoles of sodium iodide (0 5 μCi of ^{125}I) yeast particles and KRG to a final volume of 0.5 ml. tubes were incubated at 37°C and the reaction was nated after 30 min with 0 1 ml of 0 1 M sodium th phate Five ml of cold 10% trichloroacetic acid (TCA then added After centrifugation the precipitate washed three times with 5 ml of TCA The iodinatio expressed as nmoles I precipitated per 1×10^6 PML 30 min

Superoxide generation was assayed essentially de scribed by Curnutte and Babior (9) The reaction mi contained 5×10^6 PMNL 75 μM horse heart ferr chrome c (Cyt c Type III Sigma Chemical Co), serum-treated zymosan (STZ) and KRG to a final v of 3 ml The reaction was initiated by incubating the reaction mixture at 37°C in a water bath 1.5 ml kept at 0°C in melting ice and used as a blank After the test tubes were placed in melting ice and the trifuged at 4°C (750 g 10 min) The supernatant w lected and assayed for the amount of reduced Cyt c Beckman DU 2 spectrophotometer at 550 nm O amount of reduced Cyt c was calculated using an ance coefficient of 15 5 mM^{-1} cm^{-1} at 550 nm superoxide-dependent Cyt c reduction was expres the difference in Cyt c reduction between reactio tures containing no superoxide dismutase (SOD) Chemical Co) and those containing 200 U/ml These controls were run with each set of

Lysosomal enzyme release The extracellular of the PMNL granule associated enzyme β-glucosaminidase (E C 3 2 1 30) in the presence drugs was assayed from reaction mixtures similar employed for the determination of superoxide gen but in the absence of Cyt c and using the substrate 4-methyl umbelliferyl 2-deoxy 2 aceta β D-glucopyranoside (25) Maximum enzyme releas determined as the amount released by 0 2% Triton (Rohm and Haas Co Philadelphia Pa)

Cell free MPO mediated iodination MPO isolated human PMNL was supplied by I Olsson Lund, Sw The reaction mixtures contained varying concentr (0 2–10 μg/ml) of MPO 1×10^8 yeast cells 1 0 nmo NaI (1 0 μCi of ^{125}I) and 0 05 M Tris-HCl buffer pH to a final volume of 2 0 ml The reaction was initiat addition of 0 2 ml of 1 mM H_2O_2 After 15 min the re was terminated by addition of 0 1 ml of 0 1 M so thiosulphate and 5 ml of 10% TCA was added precipitate was washed three times with 5 ml of TC assayed for radioactivity



Effect of different concentrations of sulfasalazine 5-ASA (●) SP (□) or 5 ASA+SP (■) on random ...ion (top) and chemotaxis (bottom) Mean of three ...ments

...determine the type of inhibition on MPO-mediated ...on the kinetics of the reaction was studied using ... concentrations of iodide (0 05–1 0 mM) The in... mixture contained 5 μg MPO iodide (0 5 μCi ...×10⁸ yeast cells and Tris HCl to a final volume of ... The reaction was initiated by addition of 0 2 ml of H_2O_2

...-H_2O_2-halide mediated cytotoxicity The cytotoxic ...of the MPO H_2O_2 halide system was assessed es...ly as described by Clark et al (8) assaying the ⁵¹Cr ... from prelabelled mammalian target cells Human ...onic lung fibroblasts (WI38 Flow Lab Irwine ...nd) were used as target cells The tumour cells were ... in vitro in plastic Petri dishes (60×13 mm Flow ... in Eagle s modified medium supplemented with ...etal calf serum and antibiotics The cells were label... incubating them with 25 μCi of $Na_2{}^{51}CrO_4$ in KRG ...C for 1 h After washing the cells four times in PBS a ...on mixture was added containing 10 μg MPO a ...ide-generating system of 0 5 ml glucose (20 mg/ml) ...2 ml glucose oxidase (100 μg/ml E C 1 1 3 4 Sig...hemical Co) and 0 03 mM sodium phosphate buffer 7 0 supplemented with $1\ 5\times10^{-3}$ M KH_2PO_4 10^{-3} M $MgSO_4$ and 0 1 NaCl in 3 ml After 240 min ...ation at 37°C 0 5 ml samples were drawn to test ... containing 2 ml PBS kept on melting ice and cen...ed at 4 C (250 g 5 min) The supernatants were ...cted and assayed for radioactivity Maximum ⁵¹Cr ...e was determined by counting the supernatants from ...s where 0 2% Triton X 100 had been added The ...toxicity was expressed as per cent of maximum re...ble activity in duplicate samples

...ugs Sulfasalazine 5 aminosalicylic acid and sulfa...idine (supplied by Pharmacia Uppsala Sweden) were ...bilized to 1 mM in PBS and kept in the dark at 4°C

RESULTS

Effect of sulfasalazine and its components 5 ASA and SP on PMNL locomotion

The influence of the compounds on PMNL locomotion was assayed with the agarose method according to Nelson et al (22) using agarose activated serum as chemotactic stimulus

Sulfasalazine exhibits a pronounced dose dependent inhibition of random migration—0 1 mM decreases the migration to 30% and 0 5 mM abolishes it completely (Fig 1) The drug has however no effect on the chemotactic response per se since the relative increase in migration in the presence of activated serum was not changed in the presence of 0 1 mM—the decreased motility observed in the chemotactic assay was primarily due to decreased random migration 5 ASA shows no effect in either random migration or chemotaxis Neither does SP show any effect at the lower concentration (0 1 mM) most compatible with the concentration reached in vivo At the higher concentrations (0 25 and 0 5 mM) we observed a moderate but significant inhibition on random migration but no effect on chemotaxis To evaluate whether the pronounced effect of sulfasalazine is due to the sulfasalazine molecule or to the synergistic effect of 5 ASA and SP the later compounds were mixed and incubated with the cells No synergistic effect was however observed—the inhibition was the same as of SP alone (Fig 1)

Effect on phagocytosis and metabolic activity

The effects of sulfasalazine 5 ASA and SP on the phagocytic activity were assayed by counting the number of FITC labelled yeast cells phagocytozed by PMNL attached to glass slides This method permits an accurate quantitation of the number of ingested and attached particles Table I shows that only sulfasalazine at a high non physiological concentration (0 5 mM) reduced the uptake moderately by 25% ($p<0\ 025$) whereas the other metabolites had no significant effect on the phagocytosis of the IgG coated yeast particles

Phagocytosis of particles by PMNL is accompanied by an increased production of superoxide (O_2^-) (9) and hydrogen peroxide (H_2O_2) (17) Superoxide H_2O_2 and their derivatives are thought to play important roles in the microbicidal activity of the cells (3) They may also possess inflammatory mediating properties Reduction of O_2^-

Table I *The effect of sulfasalazine (SASP) and its metabolites 5 ASA and SP on PMNL phagocytosis superoxide production and lysosomal enzyme release*

Mean ± S D range and no of experiments in parentheses

Supplements (mM)	Phagocytosis*	Superoxide generation[b]	Lysosomal enzyme release[c]
–	3 25±0 46 (5) (2 83–3 78)	26±4 (3) (22–29)	100
SASP 0 5	2 46±0 10 (5) (2 41–2 56)	16±5 (3) (11–21)	72±6 (3) (67–78)
0 1	3 39±0 52 (3) (2 79–3 92)	24±6 (3) (17–29)	88±5 (3) (83–93)
5 ASA 0 5	3 27±0 42 (5) (2 58–3 83)	28±4 (3) (23–32)	87±9 (3) (81–95)
0 1	3 42±0 62 (3) (2 81–4 24)	28±4 (3) (24–33)	87±6 (3) (83–93)
SP 0 5	3 08±0 59 (5) (2 37–4 12)	7±2 (3) (6–7)	70±7 (3) (63–76)
0 1	3 20±0 60 (3) (2 80–3 78)	17±2 (3) (15–18)	85±9 (3) (74–95)

* Expressed as the mean number of yeast particles ingested per PMNL 100 cells were counted in each duplicate experiment
[b] Expressed as SOD-inhibitable Cyt c reduction (nmoles of reduced Cyt c/5×10⁶ PMNL 30 min)
[c] Expressed as % of the enzyme release from PMNL in the absence of drugs

tion by SOD (20) and other drugs (19) is found to lead to reduced inflammatory response Table I shows that 0 5 mM of sulfasalazine reduces the roxide anion production moderately (to 62% 01) 5 ASA shows no effect whereas 0 5 and mM of SP inhibit the superoxide activity with % and 36% respectively ($p<0.01$)

Effect on the MPO mediated iodination

When inorganic iodide is incubated with PMNL during phagocytosis a portion of the iodide is converted to a TCA precipitable protein bound form This reaction reflects a complex sequence of reactions related to oxidative activation internalization degranulation and MPO activity (18) Fig 2 shows that sulfasalazine has no significant effect on the MPO mediated iodination 5 ASA inhibits the iodination reaction only at a high concentration (0 5 mM) whereas concentrations comparable with therapeutic levels have no effect In contrast SP exhibits a dose-dependent inhibition even at low

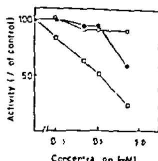


Fig 2 Effect of sulfasalazine (O) 5-ASA (●) and SP on the MPO-mediated iodination in PMNL. Mean of experiments

concentrations—0 05 mM inhibits the iodination 60%

To further elaborate on the mechanism of inhibition we studied the effect of 5 ASA and ... a cell free system using partly purified MPO inhibits the MPO mediated reaction in a dose pendent manner compatible with the inhibition ... ing intact cells (Fig 3) 5 ASA on the other ... *inhibits the reaction strikingly at a concentr*... >0 1 mM whereas 0 05 mM has no effect ... ic studies using varying concentrations of ... (0 05–1 0 mM) 5 ASA shows a non-compe... and SP a competitive type of inhibition

Effect on lysosomal enzyme release

The release of the lysosomal enzyme β-N-acet... glucosaminidase was measured after challenge ... STZ

Table I shows that 0 5 mM sulfasalazine ... the STZ-stimulated lysosomal enzyme release ... PMNL to 72±6% ($p<0.01$) of the controls ... or SP had no significant effect on this reaction

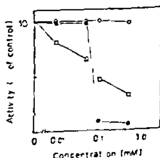


Fig 3 Effect of sulfasalazine (O) 5-ASA (●) and SP on the MPO-mediated iodination in cell-free system M... of three experiments

ble II Effect of 0 2 mM of sulfasala ne (SASP) 5 ASA and SP on the MPO–H_2O_2–hal de cytotox ci ty of human fibroblasts

± SD range and no of experiments in parentheses

Additions	Cytotox c ty
MPO–H_2O_2–Cl	48 7+3 5 (3) (46 1–53 6)
H_2O_2–Cl	18 3+2 2 (3) (16 4–20 1)
MPO–H_2O_2–Cl +SASP	50 0+2 5 (3) (47 3–52 4)
MPO–H_2O_2–Cl +5 ASA	32 4±5 2 (3) (27 1–36 2)
MPO–H_2O_2–Cl +SP	31 9+4 8 (3) (27 2 36 5)

Expressed as % Cr rad oact v ty released of max mum release from Triton X 100 (0 2%) treated fibroblasts after hours of incubation

pharmacological concentrations whereas 0 5 mM enhances the release to 70+7% ($p<0.01$)

Effects of the MPO med ated cytotox c ty on fibroblasts

The MPO H_2O hal de system takes part not only in intracellular m crob oc dal act v ty of the neutrophils During phagocytosis both MPO and H_2O_2 are released into the extracellular fluid and the MPO H_2O_2 hal de system has been reported to be toxic to certa n mammal an cells (18) and may thus mediate the inflammatory process Us ng human fibroblasts labelled with [5] Cr as target cells we studied the effects of sulfasalaz ne 5 ASA and SP on the MPO H_2O_2 hal de cytotox c system (Table II) As expected from the nh b tory effect on the MPO med ated iodinat on both 5 ASA and SP reduced the cytotox c effect of this system whereas sulfasalaz ne has no effect In fact higher concentrations (0 5 mM) of sulfasalazine and 5 ASA seem to render the target cells more vulnerable to the attack of the MPO system (not shown by figures)

DISCUSSION

Although sulfasalaz ne has been used successfully for many years in the treatment of ulcerat ve col t s its anti nflammatory act on is far from understood In animal models sulfasalaz ne has been shown to inhibit formaldehyde dextran and seroton n induced oedema (13 31) Furthermore the drug can inh bit protease activity (7) some of which is involved in the development of inflammatory reaction by d rect tissue damage or by generat ng chemotactic factors Sulfasalaz ne also exh b ts immunosuppressive activity by inh b t ng delayed hypersens tiv ty rejection of sk n transplants and lymphocyte cytotox c ty probably through a tox c act on on the effector cell (7 16) Pat ents suffering from ulcerative colitis often show an elevated number of EAC rosetting B lymphocytes This elevat on is normalized following sulfasalazine therapy (10) There is however no effect in v tro of sulfasalaz ne 5 ASA or SP on phytohaemagglut n n responsiveness or rosette format on In several stud es sulfasalazine and its metabol tes have been shown to interfere w th prostagland n metabol sm thus influenc ng the inflammatory react on Butt et al (6) and Gould (14) showed that sulfasalazine and 5 ASA inh b ted prostagland n synthes s Recently Moore et al (21) showed that sulfasalaz ne has an inh b tory effect on prostagland n E_2 and $F_{2\alpha}$ metabol sm but a very weak inh b tory effect on prostagland n synthes s They also found that ne ther SP nor 5 ASA was active on the prostaglan d n synthes s in concentrat ons that can be ach eved after oral adm n strat on of sulfasalaz ne The reduct on of the elevated prostagland n levels n the stool of ulcerat ve col t s pat ents follow ng sulfasalaz ne therapy (14) may however be secondary to reduced inflammatory response and granulocyte accumulation

Table III *Effect of sulfasalaz ne (SASP) 5 ASA and SP on d fferent stages n the PMNL funct on*

↓ Pronounced nh b on at pharmacological concentra t ons ↘ =moderate nh b on o effect at h gh concentra t ons of the drugs 0 no effect

PMNL func on	SASP	5 ASA	SP
M gra on			
Random	↓	0	↘
Chemotax s	0	0	0
Phagocytic uptake	↘	0	0
MPO od na on			
In racellular	0	↘	↓
Ex racellular	0	↓	↓
Supe ox de generation	↘	0	↘
Lysosomal enzyme release	↘	0	
Cytotoxic y	0	↓	

Most of these accumulated data point to a general anti inflammatory action of sulfasalazine and its metabolites No information is available regarding their influence on the function of PMNL—the major effector cell in the inflammatory response Several consecutive steps are involved in the PMNL activity Inhibition of any or some of these steps would result in reduced inflammatory response and tissue damage In the present investigation we can show that in concentrations comparable to pharmacological doses sulfasalazine 5 ASA and SP interfere with vital functions of the PMNL such as migration superoxide production MPO mediated iodination and cytotoxicity (Table III) It is evident that both 5 ASA and SP may modulate the inflammatory response It is also clear that sulfasalazine (or SP) is not just a vehicle for delivering its active compounds in the colon as suggested by Azad Khan et al (2) but may exhibit anti inflammatory activity in its own right Although cleavage of the azo bond occurs in the colon the intact sulfasalazine molecule is absorbed in the upper intestinal tract and serum levels of 0 01–0 1 mM are reached within a few hours (27) These concentrations were found to inhibit random migration in vitro

The effect of SP on MPO activity of PMNL is similar to the effect of dapsone (28)—a sulfone analogue with beneficial anti inflammatory properties in dermatitis herpetiformis and certain other dermatoses The clinical effect of SP in the treatment of dermatitis herpetiformis is also nearly as good as that of dapsone In contrast to dapsone we show that SP also inhibits random migration and O_2 production This may however be due to the higher ... cal concentrations of SP used The ... of SP on PMNL activity and the beneficial ... sulfones such as dapsone as an alternative ... of Mb Crohn (30) indicate that the sul... e moiety of sulfasalazine besides acting as a carrier for the 5 ASA molecule may contribute to the action of sulfasalazine in the treatment of ulcerative colitis Furthermore indirect evidence suggests that sulfones such as dapsone may interfere with the generation of chemotactic factors in certain immune complex linked dermatoses We are now pursuing this idea further

According to the original design of sulfasalazine the intention was to combine an antibacterial and an anti inflammatory agent (29) In view of the results of the present investigation we rather consider the therapeutic effect of sulfasalazine to be the result of the concurrent action of the three compounds (... fasalazine, 5 ASA and SP) with somewhat diffe... and complementary actions on the inflamma... response in the intestinal tract Whereas sul... salazine may function systemically and inter... with the recruitment of PMNL to the site of in... flammation 5 ASA and SP could modulate the ... response and tissue damage by interfering ... superoxide production MPO medi... and prostaglandin metabolism T... tion could also explain the effect of sulfasal... on cutaneous lesions characterized by vasc... and granulomatous lesions e g pyoderma ... grenosum However before a firm explanation ... be put forward for the action of sulfasalazin... inflammatory reactions in the intestinal ... effect on other cells such as macrophages ... eosinophil granulocytes has to be investigated ... though the PMNL dominates the lesion desc... above the effect of the drugs on other inflamm... cells such as macrophages eosinophils and ... cells must be investigated in order to establis... overall action of sulfasalazine

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The Role of Endogenous Cortisol
in Patients with Non-Thyroidal Illness and Decreased T_3 Levels

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RACT The aim of the study was to elucidate if nous cortisol, as previously suggested, could olved in the mechanism behind the reduced T_3 levels seen in euthyroid patients with var on thyroidal illnesses The correlation between um levels of T_3 and cortisol was investigated in pitalized patients with non thyroidal illness hyperpyrexia The results showed a correla efficient of −0 94 indicating a close reciprocal tion between the two hormones Cortisol may one factor associated with the decreased T_3 en in euthyroid patients with non thyroidal The results also indicate a close parallelism the total and free T_3 levels during hyper

ds cortisol thyroid function thyroxine conver odothyronine

d Scand 206 459 1979

d serum triiodothyronine (T_3) levels are of n in euthyroid patients with various acute onic non thyroidal illnesses and after starva malnutrition (2 5 11) An altered peripheral olism of thyroxine (T_4) seems to be the most reason responsible for these decreased T_3 The triggering mechanism behind the altered olism is still unclear (4)

have recently studied a group of 49 patients non thyroidal illnesses and decreased T_3 We found that hyperpyrexia was commonly ated with the changes in T_3 (9) The aim of esent study was to further elucidate the anism behind the decreased T_3 levels in these ts with special reference to the role of en ous cortisol levels and the influence of the one binding proteins

PATIENTS AND METHODS

Sera from 42 hospitalized patients with fever caused by various non thyroidal illnesses were analyzed for the levels of T_3 T_4 T_3 resin uptake (T_3U) T_4-binding globulin (TBG) and cortisol The material has been described pre viously (9) Eight patients had to be left out due to lack of serum samples

T_3 and T_4 levels were determined by a radioimmunoas say technique recently described (10) The normal level (mean ± S D) for T_4 is 89±17 nmol/l and for T_3 1 77±0 34 nmol/l *T_3U* was determined by a commercially available kit (Quanta Count® T_3 Bio-Rad Lab Richmond Calif USA) Normal range 25–35% *Free T_3 index* was calcu lated according to the formula $T_3 \times (T_3U)/100$ and *free T_4 index* similarly $T_4 \times (T_3U)/100$ *TBG* was determined by a commercially available radioimmunoassay kit (RIA gnost®-TBG Hoechst) Normal range 10–42 mg/l *Cor tisol* was determined by a commercially available ra dioimmunoassay kit (Diagnostic Products Los Angeles Calif USA) Normal range at 8 a m 150–600 nmol/l

Body temperature when sample was drawn was re ferred to either of the following six groups >40 0 39 9–39 0 38 9–38 0 37 9–37 0 <36 9 normal (the latter in dicating that the blood sample was collected 2 9 months later when the patient was free from disease)

RESULTS

The influence of the hormone binding proteins on the levels of T_3 and T_4 at different body tempera tures was investigated by determination of the free T_3 and free T_4 indices and TBG levels The results are shown in Table I No major differences were found in mean free T_4 index or mean TBG levels at different temperatures The mean free T_3 in dex decreased with increasing body temperature as did the mean total T_3 levels previously described (9) indicating a close association between the total

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Abbreviations T_3 = triiodothyronine T_4 = th TBG = thyroxine binding globulin T_3U = T_3 resin

Act

Table I Mean values for serum TBG free T_4 index free T_3 index T_3U and cortisol at different temperatures

	Body temperature (°C)					
	Normal	<36 9	37 0–37 9	38 0–38 9	39 0–39 9	>40 0
TBG						
n	14	13	23	22	27	6
x	25 7	25 8	28 4	26 3	26 8	24 8
S E M	0 85	1 16	1 06	1 06	1 00	2.53
Free T_4 index						
n	14	13	23	22	25	7
x	24 8	29 0	25 5	25 0	24 0	27 0
S E M	1 42	2 38	1 21	1 19	1 08	2 80
Free T_3 index						
n	14	13	23	22	25	7
x	0 53	0 43	0 37	0 37	0 30	0 25
S E M	0 05	0 04	0 04	0 04	0 03	0 06
T_3U						
n	14	13	23	22	25	7
x	31 2	32 9	31 1	32 6	32 1	35 2
S E M	0 84	0 95	0 67	0 81	0 72	1 64
Cortisol						
n	14	13	23	22	27	6
x	435	673	601	830	1 005	1 275
S E M	57	175	43	83	154	321

and free hormone levels Correlation coefficient (r)=0 99

The results of the estimation of cortisol levels are also shown in Table I The correlation coefficient (r) between the mean T_3 and mean cortisol levels in the different temperature groups was −0 94

Thus the results show that the decrease in T_3 levels was not caused by variations in the levels of TBG or binding capacity of the hormone binding proteins The close reciprocal changes in T_3 and rtisol levels indicate that cortisol may be involved the mechanism behind the decrease in T_3 levels

DISCUSSION

The present results indicate that in addition to a decreased T_3 level during hyperpyrexia a decrease in the free T_3 levels is also seen This further supports the concept of an altered peripheral conversion of T_4 and not decreased serum protein binding as the mechanism behind the changes

The triggering mechanism(s) causing the altered conversion is still unclear Administration of corticosteroids has been shown to inhibit the peripheral conversion of T_4 to T_3 (3 13) Even if the doses of corticosteroids in these studies were unphysiologically high an increased secretion of corticosteroids has been one of the factors considered responsible for the decreased T_3 levels in patients with non thyroidal diseases (6 7 12 13)

Our previous observation (9) of a close relationship between hyperpyrexia and T_3 together with the observation of a close asso between hyperpyrexia and cortisol levels (14 cates a correlation between T_3 and cortisol The results from the present investigation demonstrate such a close association Ther cortisol may be involved in the triggering nism

However opposing such an involvement tisol is the observation that no diurnal rhythm is seen despite a five fold daily change in c levels (1) Furthermore it was recently onstrated that a reduction of T_3 levels was patients with acute myocardial infarction w evidence of increased cortisol levels (8) myocardial infarction is one of the serious ill which is accompanied by decreased T_3 Therefore if cortisol is involved in the trig mechanism it cannot be the only facto

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Table I *Diagnosis of acute DVT Comparison between phlebography and thermography (N=55)*

	Phlebography	
	Pos	Neg
Thermography		
Pos	19	3+5 susp
Neg	1	27

Agreement 84%

Venous plethysmography

This was carried out with an air filled plethysmograph as described by Dohn (9) and modified by Graf and Westersten (10) Venous volume was defined as the increase in calf volume 2 min after application of a proximal venous occlusion pressure of 60 mmHg Venous outflow capacity was defined as the rate of the decrease in calf volume after release of a venous occlusion pressure of 60 mmHg and determined from the steepest part of the slope in the record curve

Phlebography

Ascending phlebography was performed according to Greitz (11)

RESULTS

An acute thrombosis was diagnosed by thermography in 22 cases and 5 thermographic pictures aroused suspicion of thrombosis Phlebography demonstrated an acute DVT in 20 patients and in only one of these the thermography was negative Thus an agreement of 84% was achieved (Table ... e difference between the two methods was ... se positive thermographies in 3 cases ... dly false positive thermographies in 5 ... d a false negative thermogram in one case ... of the 3 patients with false positive thermo... ms had recently been meniscectomized and one ... ad generalized arthritis Three of five patients with suspectedly false positive thermograms suffered from gonites local thrombophlebitis and a later visible hematoma respectively In one case the thermogram became negative after 24 hours and one patient developed a positive thermography after phlebography It is evident that in 6 of these 8 patients the temperature rise could easily be explained by other clinical conditions than acute DVT The only patient with false negative thermogram had previously suffered from repeated thrombosis and the phlebogram showed a small thrombosis in one of the calf veins

In 10 cases, thermographically diagnosed as l... thromboses, phlebography showed that the thrombus also occupied part of the femoral vein (h... thrombosis) Six high and 3 low thromboses w... localized similarly by thermography and phlebography, constituting an agreement in localization of 47%

Table II compares the diagnostic accuracy ... localizing ability of phlebography and a combination of thermography and plethysmography W... the diagnostic agreement between phlebogra... and the thermo-plethysmographic combination ... estimated to 83% and was thus on the same level as that between phlebography and thermography alone the agreement between localization ... phlebography and the thermo plethysmographic combination was 95%

DISCUSSION

This study was designed to compare the accu... of the noninvasive methods thermography and ...thysmography with phlebography in the diagn... of deep venous thrombosis Our results dem... strate an overall diagnostic agreement of 84% ... tween thermography and phlebography Th... consistent with previous documentation (4 7 8 ... 15) It should be noted that the incidence of th... bosis in this study was as low as 36% Thus ... suspicion of acute DVT at the clinical examin... could not be confirmed by objective diagn... methods in 64% Besides illustrating the unrel... ty of the clinical diagnosis of acute DVT this s...

Table II *Diagnosis and localization of acute D... Comparison between phlebography and a combination of thermography and plethysmography (N=...*

	Phlebography		
	Pos		
	High	Low	Neg
Thermography and plethysmography			
Pos high	15	1	3+5 Susp
Pos low	–	3	24
Neg	–	1	

Diagnostic agreement 83% localizing agreement 95%

need for simple screening procedures with a
agnostic sensitivity Out of 28 cases with
e phlebography 27 (96%) also had a nega
rmography The only case of false negative
diagnosis was a patient with several
s thrombotic episodes and a small acute calf
rombus The frequency of false negative
s with thermography was thus only 2%
onfirms the results in prior investigations
ing the reliability of thermography in
g the presence of an acute DVT (7 8)
he other hand a positive thermographic
s with negative phlebography seems to be
ly frequent Thus 2 18% false positive
rams have been reported in other studies
5) Several inflammatory conditions such
erficial thrombophlebitis erysipelas he
s arthritis and tendovaginitis are known
a temperature rise located to the affected
d could lead to a false positive thermo-
diagnosis (4 8 15) We report 3 clearly and
tedly false positive thermographies but 6
ese 8 patients had a clinical picture which
plain the rise of leg temperature and could
diagnosed This emphasizes the need for a
clinical examination as a basis for the
ation of the thermogram
calization of an acute thrombosis is impor
the choice of therapy in many cases de
n the extension of the thrombus Thus
therapy should be considered in cases of
mbosis limited to the calf or popliteal veins
rombolytic therapy should be considered in
f high thrombosis extending to the femoral
our investigation thermography incorrect
osed a low thrombosis in 63% of cases
hlebography showed a high thrombosis
consistent with the finding of Bergqvist
)

der to improve the localizing ability it was
to combine thermography with plethys
hy a noninvasive method with well docu
abil ty to diagnose DVT affecting the ve
utflow capacity of the popliteal and/or fem
ns (1 5) We found that this noninvasive
ic couple could both diagnose and localize
te DVT with a high degree of confidence
the agreement between localization by phle
hy on the one hand and the combination of
graphy and plethysmography on the other

Our results indicate that in the 27 patients with both negative phlebograms and thermograms phlebography was not required for diagnostic pur poses In 6 of the 8 patients with false positive thermograms and with obvious clinical find ngs explaining the temperature rise phlebography m ght also have been omitted Phlebography can then be reserved for paitents in whom thermo-graphy and plethysmography do not give conclusive results and in whom thrombolytic therapy is consid ered—only a minority of paitents according to our experience For this reason we estimate that up to 3/4 of our patients could have been spared from phlebography In our opinion the noninvasive combination of thermography and plethysmography could to a considerable extent be used as an alter native to phlebography in the routine diagnosis of acute DVT

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Non-Invasive Methods in the Evaluation Obliterative Disease of the Subclavian or Innominate Artery

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ICT The preoperative investigation of 25 referred for evaluation of subclavian artery ion is reported Non invasive methods were or to angiography to assess arm circulation direction of blood flow in the vertebral retrograde flow in one vertebral artery was 18 patients but only 7 had symptoms judged used by the reversal of flow In only one as the arm circulation so impaired as to e diagnosis of arm claudication A high fre of carotid lesions was found on the an

The report demonstrates that in cases of subclavian steal and/or arm claudication subclavian artery obliteration non invasive should be used to screen the patients before phy In many cases it will be found that s cannot be attributed to steal or impair the arm circulation and therefore angio- not indicated However, in some cases signs istent carotid lesion may still necessitate an y

s non invasive diagnosis subclavian artery e artery stenosis occlusion obliteration sub- eal

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tive disease of the subclavian or innominate ay lead to altered hemodynamics to the arm brain A significant stenosis or an occlusion ubclavian artery will cause a decrease in the ressure (BP) distal to the obliteration and the low capacity of the arm may be impaired fatigue or ischemic pain during arm work ed sensitivity to cold has also been de

The blood flow in the vertebral artery may rsed especially during arm work (Fig 1) In lation a steal of blood flow from the brain has been assumed (4 11 17) which might elicit a vertebrobasilar ischemia with symptoms such as vertigo visual disturbances ataxy contralateral motor and sensory disturbances headache and drop attacks (14 16)

During the last 15 years more than 90 patients have been operated on for obliterative disease of the subclavian or innominate arteries at the Thoracic Surgical Clinic Karolinska Hospital (12) However a still greater number have been referred for evaluation for the disease According to own experience as well as that of others (2 14) in many of the patients the symptoms cannot be ascribed with certainty to the subclavian obliterations and often a coexisting carotid lesion is the more likely cause

We investigated 25 patients by non invasive and invasive methods to elucidate how often the above mentioned symptoms can be ascribed to the subclavian stenosis or occlusion The question is of practical importance since if the symptoms are not related to an obliteration operation should not be considered and angiography not performed The findings were considered to indicate operation in 8 of our patients and the results of the operation were subsequently evaluated

PATIENTS

The study comprises 25 patients 17 men and 8 women average age 60 years (range 42-71) All had a difference of at least 20 mmHg between BPs in the arms

Twelve patients were referred to hospital because of cerebral symptoms such as vertigo visual disturbances drop attacks fits of motor or sensory disturbances in the arm or leg contralateral to the arm with lower BP Four of these patients also had symptoms from the ipsilateral arm such as sensitivity to cold in one case and paresthesia three cases (group I)

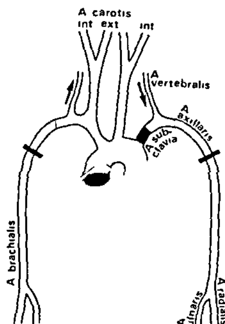


Fig 1 Flow directions in a subclavian steal

Five patients were referred for evaluation of arm symptoms Two of them had healing gangrenous ulcers in one or two fingers one complained of continuous pains in her arm and had motor disturbances one had attacks of pains from shoulder to hand at rest and in one patient arm work induced pain and the hand was extremely sensitive to cold (group II)

Eight patients were referred solely because of difference in BP between the arms and had neither cerebral nor brachial symptoms (group III)

METHODS

General investigation

The general investigation comprised a thorough penetration of the symptoms Peripheral pulses and BP were from both arms In most cases chest X ray and bicycle exercise test with ECG recordings ormed in addition

Direction of vertebral artery flow

Blood flow direction in the vertebral arteries was assessed with Doppler ultrasound as described elsewhere at rest in the sitting position *(13) A Parks Electronics Directional* flow meter 806 C with a pencil or flat probe of 5 or 10 mHz was used The probe was held by the hand against the skin over the vertebral arteries below the transversal processes of the atlas vertebra and the flow direction could be read directly from the equipment

Arm circulation

Oscillography was performed with a volume-calibrated Boucke-Brecht infracton oscillograph (1) Arterial pulsations were recorded at the upper arm at the largest circumference of the forearm at the wrist and for c parisons at the largest circumference of the calf

Systolic BP was recorded from the third finger us strain gauge according to Gundersen (7) A then placed proximally to the gauge Systolic pressu the arm was recorded with a cuff placed around the arm and the finger gauge was used for detection of ume pulse This pressure corresponded closely to pressure determined by the Korotkoff technique

Forearm blood flow was measured by venous occl plethysmography using an air filled plethysmogra 6) *with the patient in supine position* Recordings made at rest and as soon as possible (within 10 sec) maximal forearm work (see below)

Forearm work was performed dynamically on a loaded hand ergometer where the load the length and number of the springs (9) The initia was 1 25 W (7 5 kpm/m) and it was increased 1 25 W every 4th min until the patient stopped beca fatigue The work load at break point W_{max} was lated the highest load tolerated for 4 min being augm by a fraction proportional to the work time at the las load

Angiography

An angiography was performed in 21 patients The nique used at this clinic has been described earlier (some patients angiography had been performed admission

Operative technique

The subclavian and innominate arteries were structed by endarterectomy through a thoracotom Reconstructions on the internal carotid performed by endarterectomy using an extraluminal connected to an electromagnetic flow meter (3)

RESULTS

Group I (cerebral symptoms)

Arm circulation (Table I)

The systolic pressure in the diseased arm w duced to 68±14% of that of the contral and the distal pressure (dig III) to 68±17% oscillometric amplitudes over the upper arm reduced to 47±11% and over the f *52±0 14% Neither working* capacity nor blood flow at rest and shortly after work di *significantly between* the arms thus W_{max} o affected arm was 77±27% of the contrala postexercise forearm blood flow was 95±25% four patients who had symptoms also from did not differ from the other eight with pressure difference oscillometry work or postexercise forearm blood flow Arm the diseased arm did not provoke cerebra toms in any of the patients

…I Ratio affected arm/contralateral arm with regard to oscillometric index systolic pressure (strain …working capacity (W_{max}) and postexercise forearm blood flow in the three groups of patients (mean …)

	Group I (n=12)	Group II (n=5)	Group III (n=8)
…metric index			
…r arm	0 47±0 11	0 39±0 19	0 55±0 15
…rm	0 52±0 14	0 44±0 23	0 65±0 17
	0 57±0 24	0 44±0 20	0 66±0 19
…pressure			
…arm	0 68±0 14	0 63±0 10	0 71±0 08
…ger	0 68±0 17	0 61±0 20	0 74±0 08
	0 77±0 27	0 57±0 27	0 89±0 22
…cise forearm …ow	0 95±0 25	0 66±0 28	0 90±0 19

…ultrasound examination

…ade flow in the vertebral artery on the dis…de was found in 11 patients In one patient …ection was normal on both sides in spite of a …ce of 35 mmHg in BP between the arms

…aphy

…nts were examined Complete occlusion of …el on the diseased side with retrograde flow …ertebral artery was found in 9 patients Six …lusion of the left subclavian artery one of …t subclavian and two of the innominate …One of the patients with occlusion of the left …ian artery had a hemodynamic non signif…literation in the innominate artery

…ototal stenosis (left subclavian artery) was …three patients and two of them had reversed …the vertebral artery Vertebral flow direc…s in agreement with that recorded by Dopp…asound technique in all cases Carotid le…contralateral to the subclavian or innominate obstruction or bilateral were demonstrated …tients

…on for surgery and results of therapy

…rade vertebral blood flow alone was assumed …se the symptoms in three patients and the …vian artery was then reconstructed One pa…eveloped an ipsilateral hemiplegia postopera… while the other two achieved complete …omatic relief Retrograde vertebral blood …in combination with embolization from in…ate or carotid lesions were suspected of giving the symptoms in four patients In two of these complete symptomatic relief was obtained after simultaneous reconstructions of the innominate and ipsilateral internal carotid arteries In a third pa tient arm and most cerebral symptoms were re lieved after reconstruction of the left internal carotid artery but as some vertigo persisted the right subclavian artery occlusion causing ret rograde vetebral blood flow was reconstructed one year later whereupon complete relief was obtained In the fourth patient reconstruction of an innominate artery lesion relieved eye and arm symptoms but as vertigo still persists he is now waiting for reconstruction of an occlusion of the left subclavian artery causing retrograde vertebral blood flow Complete relief of cerebral and arm symptoms was obtained in two patients after recon struction of internal carotid lesions contralateral to the subclavian artery obliterations In three patients neither retrograde vertebral blood flow nor carotid lesions could explain the symptoms and these pa tients were not operated on

Group II (brachial symptoms)

Arm circulation (Table I)

The systolic pressure in the diseased arm was re duced to 63±10% of that of the contralateral and the distal pressure (dig III) to 61±20% Oscil lometric amplitudes were reduced to 39±19 and 44±23% over the upper arm and forearm respec tively Working capacity and postexercise flow were reduced to 57±27 and 66±28%

tively In one patient systolic pressure was reduced to 50% and oscillometric amplitudes to 25% The working capacity of the diseased arm was reduced and cleary limited by ischemic muscle pain Post exercise blood flow was low in relation to the work performed

Doppler ultrasound examination

Three of the five patients were examined and were all found to have reversed flow in the vertebral artery on the diseased side

Angiography

All patients were examined The left subclavian artery was occluded in two patients and stenosed in one In two patients the right subclavian artery was completely or partially occluded distally to the ver tebral artery In two patients with a left sided lesion where the vertebral artery was visualized flow di rection was in agreement with that found at ultrasound examination No pathological changes were found in the carotid arteries

Selection for surgery and results of therapy

The patient with arm claudication was operated on for an occlusion of the left subclavian artery Post operatively arm BP oscillometric indices working capacity and postexercise blood flow were normalized Two patients had healing ulcers on their fingers and were already on anticoagulant therapy They had a stenosed subclavian artery with a moderate pressure difference between the arms The lesions were due to embolization from the stenosed part of the vessel These patients were not operated on The ulcers healed and no new bolic episodes occurred In one patient with a moderate arm pressure difference angina toris was the cause of her arm pains which were ieved by nitro drugs and in another an X ray damage of the brachial plexus explained her pains and motor symptoms

Group III (without symptoms)

Arm circulation (Table I)

The systolic pressure in the diseased arm was re duced to 71±8% of that of the contralateral and oscillometric amplitudes over the upper arm to 55±15% i e to the same order of magnitude as in group I Working capacity and postexercise blood flow were not significantly reduced in the affected arm compared to the contralateral

Doppler ultrasound examination

Six of the eight patients were examined The flo the vertebral artery on the diseased side wa versed in three and normal in three

Angiography

Four patients had been examined Two had a subclavian occlusion and one a pronounced nosis In the latter patient the vertebral a branched directly from the aorta The fourth pa had an occlusion of the right subclavian artery the flow direction in the vertebral artery coul be visualized In the two patients with left occlusion the vertebral flow was reversed

DISCUSSION

In the present series comprising 25 patients subclavian stenosis or occlusion 18 had a rev flow in the ipsilateral vertebral artery bu seven had neurological symptoms that ma ascribed to vertebrobasilar ischemia Some pa with subclavian occlusive disease and a rever vertebral flow were judged to have their sym not because of steal but because of assoc carotid lesions This is in accordance with the ings of Lord et al (14) that out of 42 patients subclavian occlusive diseases and reversed fl the vertebral artery 15 had symptoms that cou ascribed to steal while 10 had sympto carotid insufficiency and 14 non specific cer symptoms

The high incidence of patients with subcl occlusive disease without reversal of ver flow or without symptoms from a reversal of tebral flow makes it desirable to examine th tients with non invasive methods before cons ing angiography

Different techniques to assess the flow dire of the vertebral arteries by Doppler ultrasound been described (8 10 13 18) In patients with cal signs of subclavian artery obliteration and bral symptoms the first measure should be to amine the vertebral blood flow direction by a invasive method

Subclavian artery obliteration relatively sel causes arm claudication (12) Nine of our pat were referred to hospital on the suspicion that subclavian artery obliteration caused arm sy toms but only in one patient was a reduced

capacity the limiting factor for arm working ity Thus in patients with arm symptoms a invasive investigation of the arm circulation evaluation of blood flow and arm working ity should be performed as the first measure

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Incidence and Significance of Heartmuscle Antibodies in Patients with Acute Myocardial Infarction and Unstable Angina

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ACT The incidence of heartmuscle anti was studied prospectively in 136 patients tively admitted for acute myocardial infarc AMI) and in 95 patients with unstable angina uscle antibodies were determinted with the immunofluorescence technique on days 1, 10, 30 in patients with AMI and on days 1 and 10 nts with unstable angina Heartmuscle an s were found in 16/136 AMI patients (12%) 13/95 (3%) with unstable angina None of the patients developed post myocardial infarction me in the 2–4 weeks after infarction or during year follow up The AMI patients with and t heartmuscle antibodies were comparable respect to age, sex, site and size of infarc incidence of early pericarditis and previous tion

ords heartmuscle antibodies acute myocardial on unstable angina

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complication following acute myocardial in on (AMI) first described by Dressler (5) in s the post myocardial infarction syndrome yndrome is characterized by the recurrence est pain and the presence of a pericardial fric ub in the 2nd–6th week after AMI associated leukocytosis a rise in temperature and in e in ESR In the following years Dressler described the condition in several publications has presented a total of 44 cases Mandel and on (17) Stein and Weinstein (18) Weiser et al Broch and Ofstad (2) and Davidson et al (4) ted identical cases during this period

The incidence of this syndrome has been reported as about 3–4% of all cases of AMI (8) In a retrospective study Broch and Ofstad (2) found an incidence of about 1%

The etiology of this syndrome is still unknown Previously extension of myocardial infarction or pulmonary embolism have been regarded as possible causes (5) Later autoimmune reaction was considered as another causative mechanism since antibodies to cardiac tissue have been found in the serum of a considerable amount (23–55%) of these patients (8 10 11 13 14 15 19) However such antibodies have also been found in the absence of the syndrome (1 10 12 16) Finally a viral etiology of the post myocardial infarction syndrome has been suggested (3 15)

To evaluate the incidence of post myocardial infarction syndrome and the true significance of heartmuscle antibodies we have designed a prospective study in which heartmuscle antibodies were determined in patients with AMI Heart muscle antibodies were also determined in patients with unstable angina

PATIENTS AND METHODS

A number of 136 patients admitted consecutively to the Coronary Care Unit because of AMI and 95 because of unstable angina were studied prospectively The diagnosis of AMI was based on a characteristic history of chest pain correlated with typical ECG changes and a serial rise in serum enzymes (LDH CPK MB and SGOT)

Infarct location was defined according to the criteria

Abbreviations AMI=acute myocardial infarction =antistreptolysin titre PBS=phosphate buffered

This study revealed that heartmuscle antibodies present in a rather high percentage (12%) of patients in 3% of those with unstable angina and only 1% of 950 healthy blood donors It is noteworthy that the two groups of AMI patients with and without heartmuscle antibodies did not differ in the size of the infarct or the incidence of pericarditis

The above mentioned data and the absence of typical post myocardial infarction syndrome suggest that heartmuscle antibodies cannot be considered as a specific and sensitive parameter for subsequent development of a post myocardial infarction syndrome However these data showed that a relation may exist between the severity of symptomatic coronary artery disease and subsequent incidence of heartmuscle antibodies Alternative explanations for the high incidence of heartmuscle antibodies might be evaluated by further immunological studies

ACKNOWLEDGEMENT

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Influence of a Myocardial Infarction on Blood Pressure and Serum Cholesterol

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RACT Blood pressure (BP) was measured be nd *after acute myocardial infarction (MI) in 21* aged 49–60 years from a random population e Men on drugs affecting BP before MI or follow up were excluded Pre and postinfarc olesterol levels were analyzed in 49 men not on ipidemic treatment recruited from the same tion sample The mean fall in systolic BP was 14 mmHg both five weeks and one year he acute event, but 10 mmHg after two years ean fall in diastolic BP (DBP) was 10 mmHg eks after the MI and remained at this level for rs *The decreases in SBP and DBP were sig* t There was a positive correlation between the um rise in SGOT during the acute phase of MI decrease in DBP between preinfarction read d readings five weeks after the MI Serum erol was unchanged three months, and one o years after the MI as compared to the prein n level

rds blood pressure serum cholesterol myocardial on

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tension and elevated serum cholesterol are nown risk factors for a first myocardial infarc MI)—primary risk factors (18 25) These fac nay also be of importance for predicting a d non fatal MI—secondary risk factors (21) studies have shown hypertension to be a sec y risk factor (26) while the importance of the terol *level is probably* less pronounced at during the first years after MI (11) though studies support its role as a secondary risk r (20) Linear and non linear combinations of vels of these and other risk factors have been to calculate the risk of MI in non symptomatic subjects (24 25) In studies of post MI patients it is *sometimes of value to estimate the risk that the* patient had run of getting his first MI before onset of symptoms based on the same risk factors Calcula tions of this multivariate risk can be used to identify low risk subjects In this category it is then possi ble to reveal other factors of importance for de velopment of an MI (10) In order to execute the calculation it is necessary to estimate the level of the risk factors before the first MI from postinfarc tion values

The purpose of this presentation is to report blood pressure (BP) and serum cholesterol levels before and after MI in a representative sample of middle aged men

PATIENTS AND METHODS

The patients were all recruited from a multiple risk factor intervention trial which has been described elsewhere (24) Briefly the study group consists of all men living in Göteborg born between 1915 and 1922 and from 1924 to 1925 The subjects were *initially randomly divided into* three groups each comprising about 10 000 men One group is the intervention group the other two serve as reference groups The screening examination which be gan in 1970 was completed in 1973 Rescreening was performed four years after the initial screening and began in 1974 At screening the subjects weight total serum cholesterol and BP were recorded The screening took place in the afternoon and the subjects were asked not to eat during four hours before the examination BP was measured in the right arm according to WHO recommen dations (17) after a five min interview in the sitting posi tion Diastolic BP (DBP) was recorded when the Korotkov sounds disappeared (phase 5)

Abbreviations MI=myocardial infarction BP=bl pressure SBP=systolic BP DBP=diastolic BP

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sible for the decrease in BP a similar decrease would be expected in cholesterol This was not the case Thus the present groups form their own group mean which again as such should not be subjected to regression to the mean

Of necessity the present analysis has been mainly limited to patients not on hypotensive drugs before and after MI Patients treated with such drugs before and/or after MI form a heterogeneous group Due to modifications on account of the infarction the therapy given before is seldom identical to that prescribed postinfarction And although a few patients did receive the same treatment before and after infarction the two conditions are not comparable because the mode of action of the drugs may differ and/or the patient s response may be changed Therefore it would be difficult to interpret pre and postinfarction comparisons in patients treated with hypotensive drugs Nevertheless the group of patients who were treated did show the same reductions of SBP and DBP when they were analyzed separately This supports the above conclusions that the present observations are not subjected to regression to the mean Therefore the demonstrated reduction of 14/10 mmHg seems a reasonable estimation of the infarction induced BP reduction at five weeks and one year after the infarction A flawless study on the influence of an MI on the BP of all patients in a series is difficult to conceive due to the necessity of treating post MI patients with e g β blockers or diuretics

The significant relationships between fall in DBP and maximum SGOT while in hospital suggests that the former is at least partly a consequence of loss of heart muscle tissue There are a number of studies iating the maximum SGOT level to the extent of damage in acute MI (5 12 21 27) Other al explanations are however not excluded

The slightly higher mean serum cholesterol in the men who subsequently suffered an MI compared with the population sample is expected because serum cholesterol is a major risk factor for MI The difference shown is a minimum since subjects with considerably higher serum cholesterol values were treated with lipid lowering drugs and thus excluded from this study

The mean cholesterol level three months after the MI did not differ significantly from the mean level at screening up to five years earlier nor did subsequent values one and two years after the MI change significantly These findings which indicate that the fall in serum cholesterol following MI is re versed within three months are in keeping with re ports based on analyses during the acute phase follow up

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Myocardıal Infarctıon Complıcated by Heart Block—Treatment and Long-Term Prognosıs

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Г A number of 597 patients with acute infarction (AMI) were treated with con G monitoring of the heart rhythm in a re unit for at least three days We found with heart block 39 with complete 29 t second degree and 16 with at most first block The treatment was primarily con of the 39 patients with complete heart given isoproterenol and two received tem makers Survival was traced over two whole patient group with myocardial Heart block implied a worsened prog e two years but survival was independ egree of heart block Among those with art block, survival did not differ from omparable patient series from Copen re all patients were given pacemakers not support indiscriminate artificial atients with AMI and complete heart results ought to be controlled in a ran dy

myocard al ınfarctıon heart block treat)sıs

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al cardıac pacemaker ıs of unquestıon n chronıc or ıntermıttent complete heart ould therefore also seem logıcal to use e frequently transıent heart block seen myocardıal ınfarctıon (AMI) Its posıtıve urvıval rates has however never been ed and has even been questıoned (4) f documentatıon and our own experıence s to adopt a prımarıly conservatıve posı cemaker treatment ın myocard al ınfarc ugh we do have the resources for thıs

pose was to study AMI patıents treated ın care unıt (CCU) who developed heart block and the survıval rate of these patıents for a perıod of two years Partıcular attentıon was paıd to those wıth complete heart block

METHODS

The study populatıon comprıses all pat ents wıth a d ag nosıs of AMI adm tted to the CCU at the Central Hosp tal ın Borås durıng 1974 and 1975 The Med cal Cl n c cares for all pat ents wıth myocard al ınfarct on among a popula tıon of approx mately 130 000 res dents Pat ents wıth s gns of a myocardıal ınfarctıon were adm tted to the CCU for at least three days pat ents wıth compl cated ınfarct for longer perıods Subsequent care was g ven n the ordı nary med cal wards

The d agnosıs of card ac ınfarctıon ıs based on stated crıterıa—symptoms ECG f nd ngs transam nase levels and autopsy find ngs A standard zed nfarctıon record ıs used ın the CCU

The d agnosıs of heart block ıs based on cont nuous mon torıng of the ECG by osc lloscope and 12 lead ECG each morn ng for at least the f rst three days ın the CCU The patıent group recorded as hav ng heart block does not ınclude those who d splayed heart block only termınally or ın d rect assocıat on w th electroconversıon of ventrıcular f brıllat on The locat on of the ınfarct n pat ents wıth heart block was determıned entırely from the ECG f nd ıngs

The treatment of all degrees of heart block was prımarı ly expectant In pat ents w th syncope or bradycard a wıth hemodynam c compl cat ons ısoproterenol ınfus on was gıven n an effort to establ sh a heart rate of approx mately 50–60/m n In patıents who d d not respond to therapy a transvenous pacemaker was temporarıly ımplanted Pa t ents w th pers stent complete heart block rece ved per manent pacemakers

The two-year survıval rate n the ent re study popula t on has been ınvest gated on the bas s of ınformatıon from hosp tal records and the central populat on reg ster

The pat ents were categorızed ın a manner somewhat sımılar to that used ın a study by Leth et al (6) from Copenhagen wh ch s the only one ava lable for comparı

Abbre at ns AMI acute myocard al ınfarct on CCU—coronary care unıt

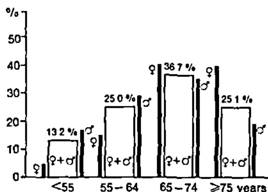


Fig 1 Age and sex distribution among 597 AMI patients

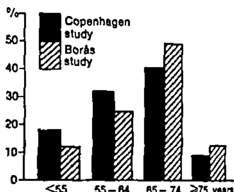


Fig 3 Age distribution among patients from Coper (6) and Borås with AMI and complete heart block

son of the long term prognosis following cardiac infarction complicated by complete heart block While we were re strictive with respect to pacing all patients with complete heart block were paced in the Copenhagen study

The variation of survival curves has been calculated according to Greenwood s estimate (1) Survival is pre sented in Fig 5 where the x axis on the quadratic figure represents fractions of observation time and the y axis fractions of the number of patients observed The area under the survival curves was calculated and expressed as a fraction of the total surface of the square This figure represents the fractional life time F_L i e survival as a fraction of the total observation time $F_D=(1-F_L)$ is the time of being dead as a fraction of the total observation time

PATIENTS

During the observation period the diagnosis of AMI was made in 602 patients treated in the CCU Five patients could not be traced for the two-year period and were therefore excluded 597 patients were thus left for the study Age and sex distribution is shown in Fig 1

RESULTS

Of the 597 patients 85 had heart block—co in 40 at most second degree in 29 at mo degree in 16 corresponding to incidences of 6 and 2 7%, or roughly 7 5 and 3% One patie admitted twice with cardiac infarction compl by temporary complete heart block but or first infarct is included in the subsequent c tions

Sex and age distribution among the 39 st with complete heart block and the location c infarctions are shown in Figs 2 3 and 4 S curves for the entire infarct population a those with heart block are given in Fig 5 a different degrees of heart block in Fig 6 Of infarctions with heart block 16 (41%) wen farctions There is no significant difference be this figure and that for patients without heart l

Fig 5 shows that at every interval over th

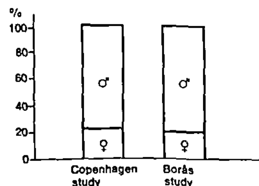


Fig 2 Sex distribution among 56 patients from Copenhagen (6) and 39 from Borås with AMI and com plete heart block

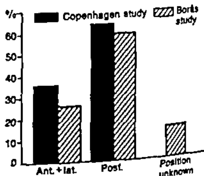
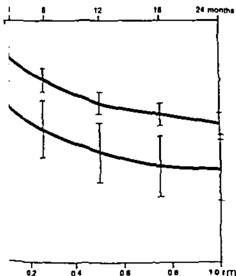


Fig 4 Location of infarctions with complete hea in patients from Copenhagen (6) and Borås A does not exclude an additional posterior infarctior



;urvival during two years after AMI among 597 (upper curve) and among those who also had ck (lower curve) Two standard deviations are

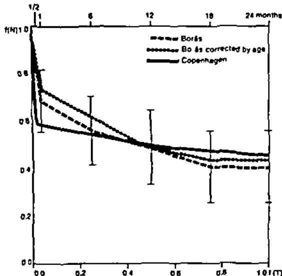
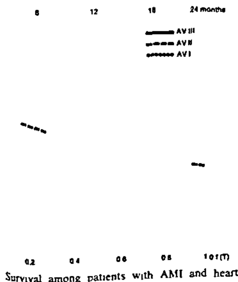


Fig 7 Survival among 39 patients from Borås with two standard deviations indicated and 56 from Copenhagen (6) with AMI and complete heart block Included is also the patient group from Borås corrected by age to the Copenhagen study

nod the patients with heart block had a ntly lower survival than all the patients in ct population Fig 6 shows that the surviv as not related to the degree of heart block gards patients with complete heart block ipared our results with those of the agen study (6) Fig 4 shows the location of



Survival among patients with AMI and heart

infarctions in the two studies Among the six cases with position unknown autopsy was performed in three and disclosed two with anterior and one with only posterior infarction Considering the few un classified patients in our series it can be said that the proportion of patients with infarction at the various locations is approximately the same in the two studies Our patients were somewhat older and for this reason we have calculated the average mor tality for each age group Using these figures a new study group was constructed with the same age distribution as in the Copenhagen study

Fig 7 shows survival rates over the two year period for the two groups compared together with the corresponding curve for our uncorrected study group The two week survival among the patients from Copenhagen is assumed to correspond to what that report terms hospital mortality Despite the differences in therapeutic principles there is no significant difference in survival between any of the three groups as observed at 1 12 and 24 months The fractional life time in our uncorrected group is 0 51 in our corrected group 0 53 and in the Copenhagen group 0 52 In accordance with our standard therapeutic procedure temporary pace makers were implanted in wo patients and a permanent pacemaker in another patient in postacute phase following persistent co

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entral and Renal Circulation, Renin and Aldosterone in Plasma during Prazosin Treatment in Essential Hypertension

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ACT The hemodynamic adaptation and the in the renin–aldosterone system during nt with a new vasodilating drug, prazosin ess®), were studied in 14 patients with essen ertension before and after 2 and 4 months of nt The mean daily dose was 2 mg/day for the months and was increased individually up to day during the last 2 months in those patients mean arterial blood pressure (MAP) remained l The reduction of MAP was mainly due to a n peripheral resistance but also to a decrease ac output in 4 of the patients Effective renal flow increased from 220 to 254 ml/min m², y as a result of a fall in vascular resistance in eys The plasma volume showed a small t increase after 2 months, from 19 0 to 20 0 ody height, whereas pulmonary plasma vol s unchanged, indicating a slight redistribu plasma between the pulmonary and the sys- rculation Body weight increased from 75 1 to which, although a crude parameter might volume expansion Plasma renin activity a small, transient increase after 2 months 46 to 0 65 nmol A_1/l h whereas plasma al ne concentration was unchanged, indicating olume expansion was not a result of a stimu enin–aldosterone system The serum sodium oride concentrations fell from 142 7 to 140 2 and from 105 9 to 103 1 mmol/l, respectively

rds hypertension heart cardiovascular system essels kidney blood volume renin

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in is a relatively new antihypertensive drug elicits vasodilation in both the arterial and nous segments of the systemic circulation (1) sulting reduction in peripheral resistance is sis for its use in essential hypertension (1 7 23 24 30) Reflex tachycardia and increased c output which are often seen during treatment with other vasodilating drugs such as hydralazine (6 12 25 33) are essentially absent during prazosin administration (25)

Messerli et al (27) studying untreated cases with borderline hypertension observed a positive correlation between cardiac output and cardiopulmonary blood volume and an inverse correlation between peripheral resistance and blood volume An increase in the systemic intravascular volume resulting from arteriolar and venous dilatation by prazosin might lead to a redistribution of blood between the pulmonary and the systemic circulation Furthermore a generalized arteriolar dilatation might lead to an increase in renal blood flow in spite of unchanged cardiac output and a fall in blood pressure The changes in circulatory pattern pressure and intravascular volume might also influence the renin–aldosterone system (9 10)

The aim of the present investigation was to study the hemodynamic adaptation and the change in the renin–aldosterone system during prazosin treatment in order to obtain a better understanding of the action of the drug when applied in the treatment of essential hypertension

PATIENTS

Fourteen patients five females and nine males 37–65 years of age (mean 49 3) were included They were informed volunteers with essential hypertension stage I or II according to the WHO classification The diagnosis was based on clinical examination blood and urine

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Abbreviations BP=blood pressure MAP=mean arterial BP [¹³¹I] OIH=[¹³¹I] orthoiodohippuran ERPF=effective renal plasma flow CI=cardiac index CI_{pl}=C plasma IVCT=interventricular circulation ti pulmonary circulation time PPV=pulmonar volume LVWI=left ventricular work index peripheral resistance index

Table I *Hemodynamic variables estimated at a 2 month interval in ten untreated patients with essential hypertension*

C=control 2 M=2 months later

		Mean	S E M
ERPF (ml/min m²)	C	257	15
	2M	238	29
Body weight (kg)	C	76 7	3 6
	2M	76 8	3 5
Plasma volume (ml/cm)	C	19 0	0 6
	2M	18 8	0 7
Blood volume (ml/cm)	C	31 0	0 9
	2M	30 5	1 2
PPV (ml/m²)	C	178	8
	2M	173	8
IVCT (s)	C	7 08	0 36
	2M	7 36	0 46
CI (l/min m²)	C	3 796	0 192
	2M	3 527	0 220
Heart rate (beats/min)	C	67 2	2 9
	2M	64 4	3 1
MAP (mmHg)	C	114	2
	2M	115	3
LVWI (W/m²)	C	0 93	0 05
	2M	0 89	0 07
TPRI (10⁵ N s m⁻²)	C	2 450	127
	2M	2 678	134
Plasma renin activity (nmol A₁/l h)	C	0 19	0 04
	2M	0 14	0 02
Plasma aldosterone (pmol/l)	C	190	17
	2M	165	19
Serum sodium (mmol/l)	C	140 7	1 0
	2M	140 0	1 5
Serum potassium (nmol/l)	C	3 96	0 12
	2M	4 13	0 12
Serum chloride (mmol/l)	C	104	1 3
	2M	106 1	0 7
urea l/l)	C	5 42	0 36
	2M	5 77	0 49

05 for all variables

analyses ECG chest X ray renography and determination of plasma renin activity and plasma aldosterone concentration before and after stimulation with furosemide In some cases urography was also performed

The reference values (mean±S D) were body height 172 7±12 4 cm body weight 75 2±14 5 kg systolic BP (sitting position) 179±26 mmHg diastolic BP 113±10 mmHg cardiac volume (X ray) 425±62 ml/m² blood urea 5 1±1 4 mmol/l serum creatinine 85 8±25 9 µmol/l

Four patients had taken antihypertensive drugs previously (alprenolol trichlormethiazide methyldopa or chlorthalidone) These drugs were withdrawn at least 4 weeks before the start of the study Three additional patients had to be excluded after a few weeks of t ment two due to technical errors and one because o potence Two of the females were menstruating wo They were both studied in their follicular phases (3")

METHODS

The patients were studied before and after 2 and 4 mo of treatment with prazosin (Peripress® Pfizer) They ambulatory and examined on an out patient basis were received in the laboratory at 8 a m afte breakfast and no previous exercise The meas re were started after 60 min rest in the supine pos tion control measurements (see below) the patien s given prazosin The daily dose was gradually incre from 0 5 mg in the first evening to 0 5 mg twice during the first week and 1 mg twice daily there During the first 2 months of treatment clinical exa tions were performed every 2nd week Six of the pat still had an elevated mean arterial BP (MAP) mmHg after 2 months of treatment The daily were increased individually up to 3 5 mg twice during the last 2 months of the study (BP control 2nd week) On days of study the drug was ta hours before the start of measurements

Renography

The individual kidney [¹³¹I] orthoiodohippuran (¹³¹I) clearance effective renal plasma flow (ERPF) was de termined with a quantitative renographic technique de scribed previously (28 29) The basis for the ERPF c lation was the net kidney uptake of [¹³¹I] OIH after a bolus injection

Cardiography

Cardiac output was estimated with a radiocardiog technique employing a gamma camera a Cine 200 ter for rapid sequential uptake and data handling ¹¹³ᵐindium transferrin as the intravascular label as ously described (11 12 13 14) Blood and plasma sa were drawn 10 20 and 30 min after the bolus injectio ¹¹³ᵐindium The specific activity of the tracer in samples allowed for calculation of tracer concentra at the time of injection

The arterial BP was measured automatically on the with an Arteriosonde (Roche)

The radiocardiographic parameters wer calculat previously described (11) The blood and plasma vol were calculated from the dose of ¹¹³ᵐIn given the sp activity in blood and plasma being corrected to bolus i tion time Cardiac index (CI) of plasma (CI$_{pl}$ ml/min was calculated from CI of blood as CI$_{pl}$=CI C where C$_b$ is the radioactivity of ¹¹³ᵐIn expressed in ml of the whole blood and C$_{pl}$ the corresponding activity expressed in cpm/ml of plasma at bolus inje time The interventricular circulation time (IVCT plasma was determined as the time between the pe the dilution curves generated for the right and le ventricles

Mean pulmonary circulation time (PCT) was cal as 70% of IVCT Pulmonary plasma volume (PPV was calculated by multiplying the CI$_{pl}$/s by PCT (

:II Changes from the control study (C) to estimations 2 (2M) and 4 (4M) months after prazosin nent (n=14)

		Mean	S E M	p
volume (ml/cm)	C	19 0	1 0	
	2M	20 0	0 8	0 05
	4M	19 8	0 7	NS
1m²)	C	163	9	
	2M	172	11	NS
	4M	171	11	NS
:)	C	7 03	0 58	
	2M	7 37	0 50	NS
	4M	7 31	0 39	NS
ight (kg)	C	75 1	3 8	
	2M	75 8	4 0	<0 05
	4M	77 1	4 0	<0 05
enin activity (nmol A_1/l h)	C	0 46	0 11	
	2M	0 65	0 11	<0 05
	4M	0 42	0 12	NS
ldosterone (pmol/l)	C	241	31	
	2M	274	25	NS
	4M	290	40	NS

significant

s calculated from systolic (SAP) and diastolic ressure as (SAP+2 DAP)/3 (mmHg) Left ar work index (LVWI) and total peripheral resist x (TPRI) were calculated as follows LVWI= n m²) MAP (mmHg) 13 6 g/cm² 1/1000] 0 16 TPRI=MAP (mmHg) 80/CI (l/min m²) (10⁵ =dyn s cm⁻⁵ m²) where 13 6 is the specific f Hg 0 16 a converting factor from kpm/min (W) and 80 a converting factor from mmHg/l/ dyn s cm⁻⁵

d reproducibility

ficient of correlation for ERPF estimated simul with constant infusion technique and the renochnique in 71 patients was 0 93 (28) Similarly cient of correlation for cardiac output measured inary dilution technique based on continuous of arterial blood and the cardiographic technique jects was 0 96 (11) The coefficient of variation d on the basis of measurements performed with ographic technique at a 30-min interval in 18 with essential hypertension was for plasma vol % CI 7 4% LVWI 10 7% and PPV 11 7% The nt of variation for EPPF was 12 5% calculated licate measurements in 38 patients with essential sion

were no statistically significant changes in the estimated at a 2 month interval in ten untreated (four males six females aged 31-57 years) with hypertension stage I or II as illustrated in Table systolic and diastolic BPs (mean±S D) were and 106±10 mmHg respectively a renin activity and plasma aldosterone were d with radioimmunoassay (31 3²) Their coefficients of variation were 6 9% and 5% respectively Blood urea serum creatinine and serum electrolytes were determined with a Technicon SMA 12/60 Autoanalyzer (Central Laboratory Aker Hospital)

The observed values after 2 and 4 months were compared with the control values using Student s *t* test for paired observations

RESULTS

As can be seen from Table I no statistical changes occurred in the variables when estimated at two-month intervals in 10 untreated hypertensive patients

Almost all patients in the treatment group reported slight sedation during the first weeks of treatment Two of them also had a tendency to orthostatic dizziness Some of the patients complained of headache and palpitations The patients were informed of possible side effects of the drug before the start of treatment and all but one volunteered to continue on the prescribed dose despite initial complaints Most side effects disappeared after a couple of weeks Prazosin was withdrawn in one patient because of impotence which disappeared after cessation of the drug As shown in Table II there was a slight increase in total plasma volume barely statistically significant after months of treatment There was a slight the mean PPV but the change was not

Table III *Changes in kidney function variables and serum electrolytes from the control study (C* *estimations 2 (2M) and 4 (4M) months after prazosin treatment (n=14)*

		Mean	S E M	p
ERPF (ml/min m²)	C	220	13	
	2M	252	13	NS
	4M	254	12	<0 05
Blood urea nitrogen (mmol/l)	C	5 1	0 4	
	2M	5 4	0 4	NS
	4M	5 3	0 3	NS
Serum creatinine (μmol/l)	C	85 5	7 0	
	2M	88 9	6 9	NS
	4M	90 7	4 6	NS
Serum sodium (mmol/l)	C	142 7	0 9	
	2M	141 0	0 7	NS
	4M	140 2	0 7	<0 02
Serum potassium (nmol/l)	C	4 1	0 1	
	2M	4 0	0 1	NS
	4M	4 0	0 1	NS
Serum chloride (mmol/l)	C	105 9	0 6	
	2M	104 9	0 5	NS
	4M	103 1	0 8	<0 02

NS=p>0 05

significant Neither was there any statistically significant change in the IVCT for plasma Plasma renin activity increased slightly after two months of treatment but fell to pretreatment levels after four months The mean value of plasma aldosterone increased but the change was not statistically significant Body weight was increased after 2 months of treatment

Table IV *Changes in systemic hemodynamic variables from the control study (C) to estimations 2 (2M) and 4 (4M) months after prazosin treatment (n=14)*

		Mean	S E M	p
(mmHg)	C	132 2	4 8	
	2M	123 0	3 9	<0 01
	4M	118 7	4 6	<0 01
I (l/min m²)	C	3 47	0 21	
	2M	3 47	0 21	NS
	4M	3 42	0 14	NS
Heart rate (beats/min)	C	71 0	3 6	
	2M	68 1	4 7	NS
	4M	65 4	2 5	<0 01
Stroke index (ml/beat)	C	50	3	
	2M	52	3	NS
	4M	53	2	NS
TPRI (10³ N s m⁻⁵)	C	3 187	189	
	2M	2 956	169	NS
	4M	2 844	168	<0 05

NS=p>0 05

As evident from Table III ERPF showed a increase after 4 months of treatment while urea and serum creatinine were unchanged S sodium and chloride both desplayed a slight statistically significant decline after 4 month treatment

The changes in the systemic hemodynamic variables are given in Table IV MAP fell in 13 of the patients The fall was mainly due to a decline peripheral resistance In 4 of the patients how the reduction of MAP was due to a fall in ca output There was a statistically significant crease in heart rate and a slight but non signifi increase in stroke volume

DISCUSSION

The observed changes in the measured vari during prazosin treatment are small The abilit the methods to detect small changes in the vari is important in the evaluation of the results Th efficients of variation as estimated from dupl determinations (see Methods) suggest that th rors and reproducibility of the methods are w an acceptable range The lack of statistical d

…s in the measured variables estimated at a 2 …th interval in ten untreated hypertensives (Ta… …) adds to the validation of the changes observed …e treatment group

…lmost all patients noticed side effects during … first days of treatment Side effects like …ache dizziness and palpitations are well …n (1 2 4 15 17) Impotence however is …ned more seldom

…here was a slight increase in total plasma vol… after 2 months of treatment whereas PPV was …anged This might indicate a small transient …e in intravascular volume predominantly in …stemic circulation It must however be re…bered that PPV is the product of cardiac out… or plasma and PCT (11) and includes the errors … these measurements The circulation time …lasma was however unchanged which indi… that the pulmonary intravascular volume was …nged (11)

…e increased plasma volume during prazosin …istration which has also been observed by … et al (18) and Koshy et al (20) taken to…r with the increased body weight might indi… water and sodium retention even if changes …dy weight constitute a crude parameter of …es in extracellular volume Volume expansion …en observed during treatment with other vaso…rs such as hydralazine (19) Furthermore the …rate fall in serum sodium and serum chloride …entrations could indicate a certain amount of … fluid dilution Masoni et al (24) also found a …ncy for serum sodium to decline in 5 patients …ed during prazosin treatment The reason for …s unknown but Maxwell (26) observed a fall in …r clearance in 4 hypertensives treated with …osin

…sodilators such as dihydralazine elicit a con…able increase in plasma renin activity (12) …ably because of secondary sympathetic stimu…n In the present study there was only a tran… increase after 2 months of treatment Hayes et … (16 17) observed a fall in plasma renin activity …ng prazosin administration The explanation …bably is that prazosin elicits a sympathicolytic …t and also a tendency to volume expansion …n is in agreement with the unchanged plasma …sterone concentration

…eports concerning the effect of prazosin on re… circulation are scanty Koshy et al (20) found … change in paraaminohippuran clearance (6 pa…tients) after 8 weeks of prazosin treatment Maxwell (26) estimated ERPF in 4 hypertensives and found a decrease in 2 and no change in the other 2 whereas Masoni et al (24) observed an increase in 5 subjects studied In the present study there was a statistically significant increase in ERPF after 4 months of treatment a rise being noted in 11 of the 14 patients This increment to the clearance of [^{131}I] OIH most likely is due to an increase in renal blood flow as a result of a fall in renal vascular resistance indicating an interference with the hemodynamic autoregulation in the kidneys This may be an important effect since renal plasma flow is reduced in patients with essential hypertension (3 5) and a further reduction has been observed during treatment with an antihypertensive drug such as propranolol (13) Blood urea and serum creatinine were unchanged This precludes gross changes in glomerular filtration rate in accordance with reports by Ibsen et al (18) Bailey (2) Curtis and Bateman (8) Maxwell (26) and Koshy et al (20)

MAP fell in all the patients due to declines in both systolic and diastolic BP This fall was mainly due to a decrease in peripheral resistance which is in agreement with previous reports (1 7 22 23 24 30) but in 4 patients it reflected a decrease in cardiac output The fall in heart rate supports the concept that prazosin elicits a sympathicolytic effect (7) in contrast to the reflex tachycardia observed during hydralazine administration (12 33)

From the present data it can be concluded that prazosin in small doses induced favourable hemodynamic changes through a fall in BP mainly reflecting a fall in peripheral resistance a reduction in heart rate an increase in renal plasma flow and no increase in plasma aldosterone concentration The transient increase in plasma renin activity was small The transient slight increase in systemic intravascular volume and the weight gain might indicate fluid retention which was not a result of stimulation of the renin–aldosterone system There was no increase in PPV indicating a small redistribution of plasma between the pulmonary and the systemic circulation A decline in serum sodium and chloride was also observed

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Malignant Hypertension—Improving Prognosis in a Rare Disease

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ACT A follow up was made of 69 patients ed as having malignant hypertension during 5 essential in 26, secondary in 39 and unclas 4 A clear male dominance was seen (41 men, en), particularly in the group with essential nsion (18 men, 8 women) The mortality in ies was less than in previously published Thus, the 5 year survival rate was 75% in the with essential and 72% in those with sec hypertension In part this was due to hae sis and renal transplantation The impor renal function at the time of diagnosis was in this study In most patients with essential sion and serum creatinine levels below 300 renal function could be maintained or im when antihypertensive treatment was insti hereas progression of the renal damage was hose with serum creatinine levels above 300 n spite of antihypertensive treatment with 3 drugs The incidence of new cases of malig pertension tended to decrease during the ob n period particularly as regards essential nsion

ds malignant hypertension prognosis survival y symptoms renal function

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nt hypertension is a serious condition Its haracteristics were defined already in 1914 hey included severe hypertension retino with papilloedema impairment of renal n fibrinoid necrosis in the kidneys and a progressive and fatal clinical course *Keith* (8) demonstrated in 1939 that the average al time for untreated patients with degree inopathy was only 10 5 months There was ly no 5 year survival in this group When antihypertensive treatment became possible early 1950s a significant reduction in mortality occurred (4 13) The progress to uraemia could be halted at least in patients who at the time of diagnosis had close to normal renal function A further improvement of the survival rate in malig nant hypertension probably due to the availability of new and improved antihypertensive agents was achieved in the 1960s Thus 50–60% 5 year surviv al was demonstrated (7) During the last decade a few studies have shown that even in patients with initially severely impaired renal function a return towards more normal levels of renal function can be obtained probably as an effect of aggressive an tihypertensive treatment (9 11)

The incidence of malignant hypertension is very low in screening examinations of various popula tions In hospital series however a certain percent age of patients admitted with hypertension can still be classified as having malignant hypertension (6)

The purpose of this investigation was to follow up all registered cases of malignant hypertension at a large medical centre in Sweden during the years 1969–76 and to evaluate the prognosis and prognos tic factors mainly renal function as well as the annual incidence of new cases of malignant hyper tension

PATIENTS AND METHODS

All registered cases of malignant hypertension fundo scopic changes of degree III or IV (Keith Wagener and Barker classification) (8) at Sahlgren s University Hospi tal in Göteborg Sweden during an 8 year period (1969–76) were studied All grade III patients had both exsudates and haemorrhages in their fundi and were therefore clas sified as cases of malignant hypertension in agreement with the WHO criteria (16)

These 69 patients (41 men 28 women) have been fol lowed up until the end of 1977 Their average age was 46 years (range16–74) Most patients 49 (71%) had IV retinopathy while 20 (29%) had degree III e changes After detailed clinical investigat

Table I *Secondary hypertension (n=39)*

	No of pats
Renovascular disease (n=18)	
Unilateral renal artery stenosis	12
Bilateral renal artery stenosis	5
Congenital anomaly	1
Renoparenchymal disease (n=17)	
Chronic pyelonephritis	6
Chronic glomerulonephritis	6
SLE nephritis	1
Congenital anomaly	1
Unspecified	3
Endocrine disorders (n=4)	
Phaeochromocytoma	2
Cushing s syndrome	1
Oestrogen (BC pill)	1

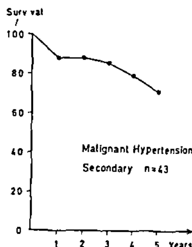


Fig 2 Survival rate in secondary (*n*=39) and unclas (*n*=4) malignant hypertension

full laboratory work up urography and in most cases also renal arteriography 26 patients (38%) were considered to have essential hypertension 39 (56%) secondary forms of hypertension (Table I) and in 4 cases (6%) a clear clas sification could not be made

These patients were followed up until the end of 1977 particularly as regards survival rate Special interest was devoted to conceivable prognostic indicators such as ini tial BP and initial renal function The survival curves were calculated by life table analysis

RESULTS

In this series of 69 patients with malignant hyper tension 19 (28%) died during the observation time The causes of death were uraemia in 10 pa tients sudden death/myocardial infarction in 4 miscellaneous in 5 No death was due to stroke

The 5 year survival rate for the patients with malignant essential hypertension was 75% (Fi and for those with secondary and unclass malignant hypertension 72% (Fig 2)

Of the 26 patients with malignant essential hy tension 20 had grade IV and 6 grade III tinopathy None of the latter patients died d the observation period and none required a therapy against uraemia The 5 year survival for the patients with grade IV retinopathy was 6 It should be noted that 4 of the latter patients derwent renal transplantation and one of t died during the surgical procedure If renal tr plantation had not been available i e if the s viving transplanted patients had died at the tim operation the 5 year survival would have 50%

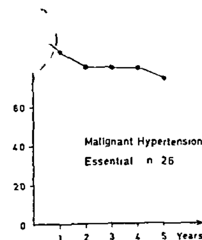
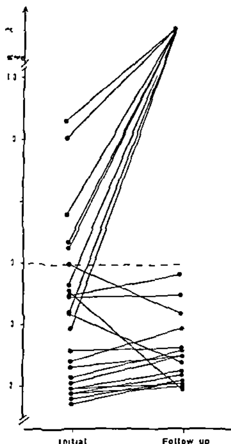


Fig 1 Survival rate in essential malignant hypertension

Table II *Blood pressure (mmHg) at the tim diagnosis (mean ±S E M)*

	Systolic BP	Diastol BP
Essential hypertension (*n*=26)	252± 4	148±
Secondary hypertension (*n*=39)	232± 5	145±
Renovascular (*n*=18)	239± 8	148±
Renoparenchymal (*n*=17)	219± 5	138±
Endocrine (*n*=4)	248±11	163±11
Unclassified (*n*=4)	258±16	150±



Change of serum creatinine in essential malignant
nsion (n=24 data from 2 patients not available)

he patients with secondary malignant hyper
n 6 with renoparenchymal disease received a transplant and 3 were treated with chronic ialysis The patients with endocrine disor (phaeochromocytoma and Cushing s syn) were treated surgically with good results
he time of diagnosis all patients had markedly d BPs (Table II) However no correlation could be found between the initial BP level and the prognosis quo ad vitam

Table III *Symptoms at the time of diagnosis*

	No of pats
Hypertensive encephalopathy	4
Stroke	2
Focal neurological signs	6
Nausea/vomiting	12
Headaches	29
Blurred vision	25
Cardiac symptoms	17
Vertigo	4
Fatigue	9
Miscellaneous	3
No symptoms	4

Among the patients with essential malignant hypertension renal function could be preserved or in some cases even improved in those who at the *time of diagnosis had serum creatinine levels below* 300 μmol/l Patients whose serum creatinine levels were above this arbitrary cut-off line all progressed towards uraemia in spite of antihypertensive therapy with three or more drugs (Fig 3)

With only four exceptions all patients presented with one or more marked symptoms in some cases severe neurological disorders in the majority however complaints such as headaches nausea and blurred vision (Table III) Another observation was the male preponderance most clearly noted in the group with essential malignant hypertension Thus 60% in the whole series were men against 69% in the group with essential malignant hypertension

Finally a non significant decrease (2×8 contingency table) in the annual incidence of malignant hypertension was seen during the observation *period* ($p=0\ 15$) (Table IV) *The entire decline* came from essential malignant hypertension

IV *New cases of malignant hypertension*

	1969	1970	1971	1972	1973	1974	1975	1976
al	5	4	5	2	3	2	3	2
	16				10			
dary*	8	5	4	4	6	4	6	6
	21				22			

ding 4 unclassified cases

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Adipose Tissue Cellularity—Metabolic Aspe

The Population Study of Women in Goteborg 1974-197

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ACT A representative population sample of aged women was studied in 1974-75 In a ple body composition and adipose tissue cel variables were determined and individuals particular clinical disorder were compared the total subsample Women with diabetes mel ad more body fat and higher fat cell weights rger fat cell numbers whereas these variables ot differ in women with IHD or hypertension red with the total subsample Total body fat ated with arterial BPs fasting blood glucose, lipids and serum uric acid The correlations stronger than those reported previously by us on weight index and these variables In univari nalyses fat cell weight correlated with systolic erum triglycerides and serum uric acid and fat umber with diastolic BP, fasting blood glucose erum uric acid In multivariate analyses, when llowance was made for total body fat the corre between these variables and fat cell weight or ll number did not reach statistical significance

ords adipose tissue body fat ischaemic heart dis population risk factors women

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ty is defined as an excess amount of body fat Enlargement of the adipose tissue mass is due reased fat cell weight and/or number (8) Pre studies have suggested that changes in fat cell t rather than in fat cell number may be as ed with aberrations in carbohydrate and lipid bolism (10 13) Recently an association be n fat cell weight and arterial blood pressure has also been suggested (9) Diabetes mellitus ension and raised serum lipid levels are as ed with an increased incidence of ischaemic t disease (IHD) (4 30 34) Hence an associa between fat cell weight and the incidence of may also be expected

A comprehensive study of the health status of middle aged women has been carried out in 1968-69 (5) and in 1974-75 (6) The study includes determination of a number of physiological and biochemical variables In a subsample data were also obtained on body composition and adipose tissue cellularity

The purpose of the present investigation was to study the relationships between total BF fat cell weight fat cell number and various risk factors for IHD For those who had IHD diabetes mellitus or hypertension and who participated in the studies of body composition and adipose tissue cellularity these data are also compared with the subsample representative of the general population

STUDY POPULATION

A population study of women was carried out in Göteborg Sweden in 1968-69 (5) and the participants were re studied in 1974-75 (6) Altogether 1 302 women were re studied in 1974-75 or 80 3% of the initial (89 1% of those studied in 1968-69 or 80 3% of the initial sample) participated in the second study Owing to the method of sampling the high participation rate and the small differences between participants and non partici pants the women who participated on both occasions are regarded as representative of the women in the general population in the age strata studied (5 6)

Body composition and adipose tissue cellularity studies in 1974-75 were carried out in a systematically selected subsample of 227 women representative of the women in the general population in the age strata studied (44 52 56 60 and 66 years of age) Of these women 199 (87 7%) attended the primary examination comprising physi cal anthropometric and laboratory investigations 153 (67 4%) took part in the body composition study and 187 (82 4%) in the adipose tissue cellularity study In the subsample fat cell weight or fat cell number did not differ with age (48) while body fat did being higher in higher

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Abbreviations IHD=ischaemic heart disease BP=blood pressure BF=body fat BW=body weight

Table I *Anthropometric data blood pressure and biochemical variables in the subsample and r population sample of women*

	Subsample			Total sample		
	n	Mean	S D	*n*	Mean	S D
BW (kg)	187	66 4	12 7	1 301	65 8	11 4
Body height (cm)	187	163 0	5 7	1 300	163 5	5 9
Triceps skinfold (mm)	187	21.5	7 0	1 298	21 1	6 7
Subscapular skinfold (mm)	187	20 9	9 9	1 298	20 5	10 0
Arm circumference (cm)	187	28 7	3 3	1 296	28 4	3 0
Waist circumference (cm)	187	78 4	10 9	1 297	77 7	10 1
Buttock circumference (cm)	187	99 1	8 9	1 295	98 7	8 0
Systolic BP (mmHg)	187	140 0	22 2	1 302	134 9	21.3
Diastolic BP (mmHg)	187	88.5	9 7	1 302	87 3	9 8
Serum cholesterol (mmol/l)	185	7 1	1 3	1 288	7 0	1 3
Serum triglycerides (mmol/l)	185	1 42	0 63	1 288	1 30	0 88
Fasting blood glucose (mmol/l)	187	5 4	0 9	1 298	5 3	0 9
Serum uric acid (μmol/l)	181	216	70	1 292	204	66

age strata (26) The anthropometric data for the subsample did not differ from the total population sample (Table I) Nor were there any differences in diastolic BP serum cholesterol or fasting blood glucose while systolic BP serum triglyceride and serum uric acid levels were somewhat higher in the subsample than in the total sample (Table I)

The correlation analyses between body composition adipose tissue cellularity and the biochemical variables and BPs were confined to the 127 women for whom all data were available Women with diabetes mellitus were excluded from the blood glucose analyses

METHODS

The women were asked to attend the primary examination after an overnight fast but were allowed to drink a moderate amount of water in the morning The research staff was the same throughout the examination period in order ze interobserver variations in measurements weight (BW) was measured to the nearest 0 1 kg wore only briefs when weighed Body height ured to the nearest 0 5 cm (27)

BP was measured with a mercury manometer a ously described (4) Serum cholesterol and ser glycerides were determined according to a modific the method of Franey and Amador (18) and Carl Wadström (14) respectively and serum uric acid ing to the method of Gochman and Schmitz (19) blood glucose was determined as proposed by Har (20)

BF was derived from data for BW total body pot and total body water as described by Berg and Is (7) The methods are described elsewhere and ar mented on together with the body composition da

Adipose tissue samples were obtained by needle according to the method of Hirsch and Goldrick C the hypogastric region (one third of the distance fr the right superior iliac spine to the umbilicus) and fr femoral region (on the anterior side of the thigh of the distance from the patella to the superior iliac The adipose tissue samples were placed in physic saline and frozen at −20°C until fat cell weight dete tion Mean fat cell weight in each region was dete according to the method of Sjostrom et al (31) T cell number was calculated by dividing total BF mean of the fat cell weights of the two regions

II *Body composition and adipose tissue cellularity in women with different clinical disorders*

	Total subsample			Myocardial infarction			Angina pectoris		
	n	Mean	S D	*n*	Mean	S D	*n*	Mean	S
BW (kg)	187	66 4	12.7	4	64 4 NS	19 0	12	65 9 NS	15
BF mass (kg)	141	20 8	7.5	4	20 9 NS	9 9	10	22 1 NS	9
Mean fat cell weight (μg)	170	0 42	0 08	4	0 43 NS	0 11	10	0 45 NS	0
Total fat cell number (×10 ⁹)	141	4 9	1 6	4	4 9 NS	2 4	8	4 4 NS	1

NS=no statistical significance $^{*}p<0.05$ $^{**}p<0.01$ $^{***}p<0.001$

II *Correlations between body composition adipose tissue cellularity and blood pressure and ical variables in the women in whom both body composition and adipose tissue cellularity data ained* ($n=127$)

	Fasting blood glucose	Serum cholesterol	Serum triglycerides	Systolic BP	Diastolic BP	Serum uric acid
	0 28**	0 09 NS	0 16(*)	0 15(*)	0 26**	0 35***
	0 26**	0 20*	0 22*	0 22*	0 30***	0 35 *
eight						
istric	0 16(*)	0 14 NS	0 21	0 17(*)	0 14 NS	0 30 **
l	0 03 NS	0 14 NS	0 02 NS	0 20*	0 14 NS	0 15( )
	0 12 NS	0 16(*)	0 14 NS	0 21	0 16(*)	0 27**
cell number	0 21**	0 16( )	0 17( )	0 12 NS	0 24 *	0 22*

ce of regression coefficients NS=no statistical significance (*)$p<0\ 10$ *$p<0\ 05$ **$p<0\ 01$ $p<0\ 001$

of angina pectoris was recorded according to a aire proposed by Rose (29) Myocardial infarc recorded as described by Elmfeldt et al (16) f arterial hypertension was obtained by inter ifest hypertension was considered to be present ect was receiving antihypertensive treatment or tolic BP ≥160 mmHg and a diastolic BP ≥95 iabetes mellitus was considered to be present if ct was receiving treatment for diabetes (diet antidiabetic drug) or had laboratory signs of fasting blood glucose concentration exceeding l)

l methods

onal statistical methods were used for calculation standard deviations (S D) correlation coeffi regression coefficients and significances of re coefficients The confounding effects of age and in the analyses of correlations between fat cell at cell number and BP and biochemical variables itrolled by multiple regression analysis Signifi differences between mean values was tested with *t* test (two-tailed) When testing mean values vith a particular clinical characteristic were com th the total subsample The differences and re coefficients were considered statistically signifi values of $p<0\ 05$

llitus	Arterial hypertension		
S D	*n*	Mean	S D
15 9	39	68 3 NS	16 0
9 7	30	22 6 NS	9 2
0 04	38	0 43 NS	0 10
1 6	29	5 0 NS	1 9

RESULTS

Body fat mass and adipose tissue cellularity in relation to IHD

Four of the women who participated in the adipose tissue cellularity study had suffered a myocardial infarction and 12 reported symptoms of angina pectoris There were no significant differences in body composition or adipose tissue cellularity between these women and the total subsample (Table II)

Body fat mass and adipose tissue cellularity in relation to risk factors for IHD

Diabetes mellitus Eight of the women who participated in the adipose tissue cellularity survey had diabetes mellitus These women had higher mean values of BW ($p<0\ 001$) BF ($p<0\ 01$) mean fat cell weight ($p<0\ 05$) and total fat cell number ($p<0\ 05$) than the women in the total subsample (Table II)

Hyperglycaemia Fasting blood glucose correlated significantly with BW ($p<0\ 01$) BF ($p<0\ 01$) and total fat cell number ($p<0\ 01$) (Table III) These correlations remained significant when allowance was made for the effect of age When allowance was also made for BF in a multiple regression analysis the correlation between fat cell number and fasting blood glucose was not significant

Hyperlipidaemia Serum cholesterol correlated significantly with BF ($p<0\ 05$) but not with fat cell weight or total fat cell number (Table III) When allowance was made for the effect of age the correlation between serum cholesterol and BF was not significant

Serum triglycerides correlated signific

BF ($p<0.05$) and fat cell weight in the hypogastric region ($p<0.05$) but not with total fat cell number (Table III) The correlations remained significant when allowance was made for the effect of age When allowance was also made for BF the correlation between serum triglycerides and fat cell weight in the hypogastric region was not significant

Arterial hypertension In the adipose tissue cellularity survey 39 women had hypertension There were no significant differences in body composition or adipose tissue cellularity between these women and the total subsample (Table II)

Arterial blood pressure Systolic BP correlated significantly with BF ($p<0.05$) fat cell weight in the femoral region ($p<0.05$) and mean fat cell weight ($p<0.05$) but not with total fat cell number (Table III) When allowance was made for the effect of age these correlations were not significant Diastolic BP correlated significantly with BF ($p<0.001$) and total fat cell number ($p<0.01$) but not with fat cell weight (Table III) These correlations remained significant when allowance was made for the effect of age When allowance was also made for BF the correlation between diastolic BP and fat cell number was not significant

Hyperuricaemia None of the women in the adipose tissue cellularity survey had a history of gout Serum uric acid correlated with BW ($p<0.001$) BF ($p<0.001$) fat cell weight in the hypogastric region ($p<0.001$) mean fat cell weight ($p<0.01$) and total fat cell number ($p<0.05$) These correlations remained significant when allowance was made for the effect of age When allowance was also made for BF the correlations between serum uric acid and the adipose tissue cellularity variables were not significant

DISCUSSION

Body fat IHD and risk factors for IHD

Earlier reports have suggested no or only a weak association between various estimates of obesity and IHD (22 23 30 34) Similar results have been reported recently concerning the relationship between BF and IHD (35) The present data agree with these reports but the number of subjects with IHD is too low to allow conclusions Multivariate analysis of data from prospective studies has shown that the effect of obesity on development of IHD is to a large extent mediated through coexisting atherogenic traits (22 23) Increased BF mass was also associated in the present study with raised serum lipids fasting blood glucose as well as raised BP levels The importance of an increased BF mass in diabetes hyperlipidaemia and arterial hypertension is also suggested by the fact that weight reduction is accompanied by an improved glucose tolerance and reduced serum lipid and BP levels (3)

Adipose tissue cellularity IHD and risk factors for IHD

In this study an attempt was made to elucidate the relative contributions of fat cell weight and fat cell number to the associations discussed above

A recent report has suggested an association between arterial hypertension and increased fat cell weight (9) We were not able to confirm this finding As has also been reported in men (25) a correlation was found between fat cell weight and systolic BP but in the present study of women this correlation was not significant when allowance was made for the effect of age which explained almost the entire variance of systolic BP A recent study on obese women (2) revealed a correlation between fat cell number and diastolic BP This finding was confirmed in the present study of randomly selected women The correlations were significant in both studies when allowance was made for the effect of age

Several haemodynamic changes have been reported in obesity including increased cardiac output and increased peripheral arterial resistance (to Furthermore a correlation has been demonstrated between adipose tissue blood flow and fat cell number (15) Since fat cell number correlated with the diastolic BP this factor may contribute to total peripheral resistance However in the present study none of the correlations remained statistically significant when BF was kept constant In the previous study (2) allowance was not made for BF

A previous report suggested that increased fat cell weight was associated with adult diabetes mellitus (12) The findings in the present study agree with this conclusion However fat cell weight has been shown to correlate weakly but significantly with plasma insulin levels in randomly selected middle aged men (10) and in obese men and women (13) No such correlation was found initially in randomly selected women (10) but was demonstrated later for fat cell weight in the abdominal region but not for other regions (24) The data thus suggest that an increased fat cell weight is associated with

esistance However a recent study of men ...ded no correlation between fat cell weight ...ng blood glucose or plasma insulin levels ...e effect of BF was considered

...ll weight has been found to be increased in ...glycеridaemic men and women (11) In ...se men a significant correlation has been ...trated between serum triglycerides and fat ...ght (33) The present study of randomly ...middle aged women showed a similar cor... for fat cell weight in the hypogastric but not ...emoral region The observation that there ...discrepancies in the relationships between ...chemical variables measured and fat cell ...m different regions may reflect regional ...c variations as has also been reported re... 17)

...eral the present study shows stronger cor... between BF mass and arterial BP serum ...sting blood glucose and serum uric acid ...se reported between weight index and these ...s (27) The study also indicates that fat cell ...s correlated to systolic BP and serum tri...s while fat cell number seems to correlate ...stolic BP and fasting blood glucose The ...rly show that total BF is a stronger deter... or these variables than either fat cell weight ...l number alone In epidemiological studies ...m population samples it thus seems suffi... study total BF rather than adipose tissue ...y to evaluate the impact of obesity on

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Hyperparathyroidism Associated with Distal Tubular Dysfunction
...t Intact Reabsorption of Protein in the Proximal Tubules

Lars Wibell Per Anders Dahlberg and Anders Karlsson

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...T The urinary output of β_2-microglobu... ...asured in ten hypercalcemic patients un... ...urgery because of hyperparathyroidism ...bjects the β_2-microglobulin excretion was ... increased and in seven patients it was ...fore surgery Three of these seven pa... ...layed markedly impaired distal tubular ...ith a reduced urinary concentration capac... ...urgery all patients became normocalcemic ...inary concentrating capacities improved ...roglobulin excretion on the other hand ...unchanged Thus, hypercalcemia per se ...adily affect the proximal tubular function ...bing low molecular weight proteins "Tu...einuria", if found in patients with hyper... should be suspected to reflect damage to ... by additional mechanisms

... hyperparathyroidism hypercalcemia β_2 ...lin kidney function

...cand 206 507 1979

...athyroidism (HPT) is sometimes ac... ...d by kidney dysfunction in general attrib... ... diffuse calcium nephropathy (8) When ...rular filtration rate is impaired (14 18) it ...nproves after parathyroidectomy In con... ... common impairment of the renal con... ...g ability is often reversed after correction ...percalcemia (7 11)

...been claimed (6) that a selective urinary ...n of low molecular weight (LMW) proteins ... proteinuria can be present in patients ...T—and be reversible during the months ...g parathyroidectomy Hayslett et al (13) ...scribed three hyperparathyroid subjects ...mal serum creatinine values and increased ...ns of lysozyme (mol wt 14000) Revillard et al (20) have found mixed proteinuric patterns by electrophoresis of urinary protein in five patients with parathyroid adenomas

We have investigated the influence of hypercalcemia on the proximal renal tubules by following the urinary output of β microglobulin in patients undergoing surgery because of HPT β microglobulin (mol wt 11800) first isolated from the urine of patients with renal tubular disorders (4) is one of the major LMW proteins of tubular proteinuria and as such a sensitive marker of protein reabsorption in the proximal renal tubules (19 23)

PATIENTS

Ten patients with hypercalcemia and probable HPT were selected for the study Patients with a history of recurrent kidney stones or infections in the urinary pathways were excluded since obstruction and infection particularly if connected with hypercalciuria or renal tubular acidosis may be associated with an abnormal excretion of LMW proteins (5 12 13 15) In seven of the patients a diagnosis of HPT was not suspected until a routine serum calcium determination was performed and disclosed a high value Patients 3 and 8 had suffered single episodes of renal colic These patients and patient 9 had minimal kidney calcifications at urography Patient 5 had a non functioning left kidney after a complicated nephrolithotomy 15 years ago In all other patients X ray investigations of the kidneys were normal

Laboratory findings are presented in Table I Pronounced hypercalciuria was present in patients 1-3 and moderate hypercalciuria in two of the other seven subjects Most patients had an increased phosphate excretion and when tested in patients 5-10 pathological urine phosphate responses to calcium infusion as in HPT (22) were found in five cases The ability to produce concentrated urine was subnormal in all subjects and markedly low urinary osmolalities were noted after pitressin tannate administration in patients 1-3 Serum alkaline phosphatase

Abbreviations HPT = hyperparathyroidism LMW ... molecular weight

Table I *Laboratory findings*

With the exception of tubular reabsorption of phosphate (TRP) and maximal osmolality the laboratory data rep[illegible] mean of 2–5 determinations

Pat no	Sex	Age (y)	S-Ca (mmol/l) Preop	S-Ca (mmol/l) Postop [a]	U Ca (mmol/ 24 h)	Max osmol [b] (mOsm/kg)	S-creat (μmol/l)	C_{creat} (ml/min/ 1 73 m²)	S-[illegible]
1	♀	53	3 4	2 3	15	375	82	80	0 6
2	♀	51	3 3	2 4	17	530	70	120	0 6
3	♀	52	3 1	2 5	15	465	72	140	0 7
4	♀	73	3 0	3 5	5	670	110	70	0 [illegible]
5[d]	♂	66	3 0	2 5	2	630	187	45	0 [illegible]
6	♀	72	2 9	2 5	4	690	83	60	0 [illegible]
7	♀	68	2 9	2 3	10	600	75	70	0 [illegible]
8	♀	26	2 9	2 4	8	780	75	115	0 [illegible]
9	♂	64	2 9	2.3	6	680	76	95	0 [illegible]
10	♀	69	2 8	2 4	3	710	106	55	0 [illegible]
Reference values			2 2–2 6		0 6–5 0	>750	64–106	75–150	0

[a] Determined 5 months after surgery
[b] Determined with a Knaur Osmometer Urine collected after water restriction and injection of pitressin tanna[illegible]
[c] Determined after infusion of calcium (22) N = normal P =pathological
[d] This patient who had only one functioning kidney displayed moderate proteinuria (0.5 g albumin/24 h) a[illegible] glomerular filtration rate

was slightly elevated in two patients X ray investigations of the skeleton revealed an unequivocal bone disease in patient 10 with osteopenia and subperiosteal erosions Vascular calcifications of the Moenckeberg type (21) were apparent in patient 3

The diagnosis of HPT was corroborated in all patients by thorough examination of removed parathyroid tissues Expert evaluation of parathyroid glands was performed by L. Grimelius Single adenomas were found in 9 patients one of whom also had two hyperplastic glands one patient had two hyperplastic and two normal glands Postoperatively the levels of serum and urinary calcium were normalized in all patients When investigated five months [illegible]stoperatively the urinary concentration ability after [illegible]ssin tannate administration was improved in all ten [illegible]jects although in six patients the values of urinary osmolality were still subnormal in the range of 650–750 mOsm/kg

METHODS

β_2-Microglobulin was determined with a radioimmunoassay kit (9) (Phadebas Pharmacia, Uppsala) All other analyses were carried out with the routine procedures in use at the Laboratory of Clinical Chemistry University Hospital Uppsala. Only single urine specimens with a pH above 5 8 were accepted for study since at low pH degradation of β_2-microglobulin frequently occurs (10) Urines were stored at −20°C until analysis The urinary excretion of β_2-microglobulin was expressed as a ratio of β_2-microglobulin to creatinine in order to minimize the variation among samples caused by differences in diuresis (23)

RESULTS AND DISCUSSION

The urinary β_2-microglobulin/creatinine ra[illegible] before parathyroidectomy during the postop[illegible] days and at the follow up five months po[illegible]tively are shown in Fig 1 Before surg[illegible] excretion of β_2-microglobulin was of norm[illegible]nitude in seven patients Three of these pa[illegible] (nos 1–3) had the most pronounced hyperca[illegible] and hypercalciuria and the lowest maximal [illegible] osmolality after pitressin tannate adminst[illegible] At the follow up these seven patients ha[illegible] microglobulin excretion similar to that found [illegible] the operation Thus patients with HPT ma[illegible] hypercalcemia hypercalciuria and a reduce[illegible] centration capacity but still retain a normal ca[illegible] for reabsorption of LMW proteins in the pr[illegible] renal tubules

Three of the investigated patients cases 5[illegible] 10 had an abnormal excretion of β_2-microglob[illegible] It is clear that the amount of β_2-microglobulin [illegible] urine of these cases did not correlate to the [illegible] calcium level or to the maximal urinary osm[illegible] This supports the concept that an impair[illegible] centrating capacity is secondary to hypercal[illegible] and in part due to functional changes [illegible] to structural alterations and microscopic n[illegible] calcinosis in the kidney (3 8 11)

After Ca++	S alk phosph (μkat/l)
–	4 5
–	4 5
–	4 3
–	2 6
75 N	2 2
87 P	6 4
77 P	3 4
83 P	2 1
86 P	8 6
77 P	5 5
	0 8–4 8

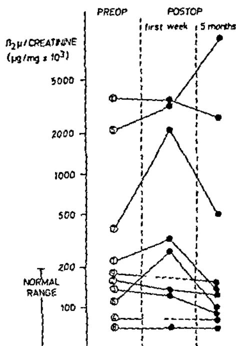


Fig 1 Urinary excretion of β_2 microglobulin before and after parathyroidectomy in ten patients with primary HPT The data are presented as the ratio of β_2-microglobulin/creatinine

mporary postoperative increase in the β_2 obulin excretion was observed in three pa ios 1 6 and 7) This finding may be analog the high excretion of LMW proteins ob in patients after major surgical intervention d in patients with large burns (1) The sm of such proteinuria is not known Possi e postoperative catabolic phase induces a n the kidney of LMW substances Such les could interfere with proximal tubular n in much the same way as an infusion of mino acids causes tubular proteinuria (17)

evious reports (6 13 20) on LMW pro- in patients with HPT no details were given ing renal stones or associated kidney dis n patients with kidney stones but without surprisingly high incidence—up to 80%—of proteinuria has been reported as lysozymuria hyperinsulinuria (5) In the latter of these all patients had spinal cord injuries Thus al pyelonephritis is likely to have been a n finding In a recent study of consecutive s with recurrent stone disease seen in patient clinic (2) less than 10% of the pa displayed an elevated excretion of β_2-micro- n

results suggest that hypercalcemia per se does not interfere with the protein reabsorbing capacity of the kidney tubules As reabsorption of filtered proteins mainly occurs in the proximal tubules (16) our findings are consistent with the observations that pathological calcifications in hypercalcemia first occur in the distal part of the nephron, such as the collecting ducts and the ascending limb of Henle s loop (8) Clearly tubular proteinuria is not an early or obligatory finding in patients with HPT When LMW proteinuria is found a complicating kidney disorder should be looked for

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Labetalol-Induced Peyronie's Disease?

A Case Report

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T Peyronie s disease (induratio penis as been observed in a 58-year old man 8 ter initiation of treatment with the new α and β blocking agent, labetalol During nonths before onset of symptoms he had 00 mg labetalol daily He showed no other normal fibrous tissue production and the as negative Cessation of the drug revealed ement Peyronie s disease has also been n relation to treatment with propranolol nd metoprolol and might be due to an alance between α and β receptors in con ue, but there may also be an immuno- s for the fibrosis A possible coincidence as the ages of the reported cases are with e where this disease most often develops

Peyronie s disease β blockers labetalol
cand 206 511 1979

disease or induratio penis plastica is al fibrous tissue production on the shaft is Although several suggestions have its aetiology is unknown (2 11) The syndrome was in some cases associated onormal fibrous tissue production in the cavity (3 6) and recently Peyronie s s been observed in relation to treatment anolol (7 12) and metoprolol (14)

should always be paid to new drugs o avoid undesired reactions for instance s to the practolol syndrome As we have the development of Peyronie s disease atment with the combined α and β block labetalol we would like to report this

CASE HISTORY

it a 58 year-old man was admitted to a long dy on the efficacy of labetalol in the management of patients with severe and resistant hypertension He had been treated for several years with methyldopa and diuretics Treatment with labetalol was initiated with 100 mg t i d and the dose was titrated against BP response and side-effects His symptoms begun 8 months after his entry to the study At that time he had been treated with labetalol 2400 mg/day for 2 months The disease made him unable to perform sexual intercourse while it did not interfere with miction The plaque measured 1×3 cm and was located on the left dorsolateral side of the shaft easily palpable

Cessation of the drug did not result in any improvement Further clinical and laboratory investigations showed no signs of abnormal fibrous tissue production elsewhere in the body especially he had no oculomucocutaneous eruptions or Dupuytren s contracture and the ANF test was negative

DISCUSSION

The age of our patient and of those cited above (7 8 12) is within the range when Peyronie s disease most often develops The observation of this disease in relation to treatment with β blocking agents may therefore be a coincidental finding without any association to the drugs employed Moreover atherosclerosis has been suggested to be an aetiological factor in Peyronie s disease (11) and as hypertension is one of the main risk factors for atherosclerotic disorders this disease might have contributed to the development of Peyronie s disease

On the other hand Pryor and Khan (8) very lately reported their results from a review of 146 patients with Peyronie s disease Of these patients 19 (13 1%) had been treated with a β blocking agent against none of the age matched controls without this disease Of the 19 patients 7 had been receiving practolol and 13 propranolol including one patient on both drugs for at least six months before the onset of penile discomfort The mean age patients was 55 years (range 25–72) but nately no information is given either

the patients on β blocking agents or whether they had concomitant atherosclerotic diseases or hyper tension However the findings in this large series seem to suggest a relationship between therapy with *β blocking agents and onset of Peyronie s disease* in some patients

Although the practolol syndrome is well estab lished including the sclerosing conditions it is still unknown whether the abnormal fibrous tissue production is due to an impaired balance between α and β receptors in connective tissue or there *may be an immunological basis for the fibrosis* Amos et al (1) observed that practolol metabolites provoked antibody production and a positive ANF test was associated with this syndrome (4, 10) A positive ANF test has also been encountered during treatment with labetalol (9) The ANF test was negative in our patient and in this context it must be stressed that a positive ANF test does not neces sarily imply drug induction Positive ANF tests *have been found as often in untreated as in treated* hypertensive patients (5) and significantly more often in untreated hypertensive patients than in normotensive controls (5 13)

The observation of Peyronie s disease in connec tion with treatment with non selective (propranolol (7 8 12)) cardioselective (metoprolol (14) and *practolol (8)) and combined α and β blocking* agents (labetalol) thus might suggest that an altered balance between α and β receptors contributes to an abnormal fibrous tissue production However a provocation of antibody formation induced by molecular structural similarities between these drugs or their metabolites cannot be ruled out

As labetalol is about to be introduced to Scandinavian antihypertensive drug market cians are asked to pay attention to this proble

ADDENDUM

Eight months after cessation of labetalol t brous plaque had diminished markedly and t tient was again able to perform sexual interco

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